

EXHIBIT A122

IRS

Chemical Substances and Biological Agents

Studies and Research Projects



REPORT R-755



Synthesis of Knowledge on Tremolite in Talc

*Chantal Dion
Guy Perrault
Mounia Rhazi*



Established in Québec since 1980, the Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST) is a scientific research organization known for the quality of its work and the expertise of its personnel.

OUR RESEARCH *is working for you !*

Mission

To contribute, through research, to the prevention of industrial accidents and occupational diseases as well as to the rehabilitation of affected workers.

To offer the laboratory services and expertise necessary for the activities of the public occupational health and safety prevention network.

To disseminate knowledge, and to act as scientific benchmark and expert.

Funded by the Commission de la santé et de la sécurité du travail, the IRSST has a board of directors made up of an equal number of employer and worker representatives.

To find out more

Visit our Web site for complete up-to-date information about the IRSST. All our publications can be downloaded at no charge.

www.irsst.qc.ca

To obtain the latest information on the research carried out or funded by the IRSST, subscribe to *Prévention au travail*, the free magazine published jointly by the IRSST and the CSST.

Subscription: 1-877-221-7046

Legal Deposit

Bibliothèque et Archives nationales du Québec
2012

ISBN: 978-2-89631-640-3 (PDF)

ISSN: 0820-8395

IRSST – Communications and Knowledge

Transfer Division

505 De Maisonneuve Blvd. West

Montréal, Québec

H3A 3C2

Phone: 514 288-1551

Fax: 514 288-7636

publications@irsst.qc.ca

www.irsst.qc.ca

© Institut de recherche Robert-Sauvé
en santé et en sécurité du travail,
October 2012



Chemical Substances and Biological Agents

Studies and Research Projects



REPORT R-755

Synthesis of Knowledge on Tremolite in Talc

Disclaimer

The IRSST makes no guarantee regarding the accuracy, reliability or completeness of the information contained in this document. Under no circumstances shall the IRSST be held liable for any physical or psychological injury or material damage resulting from the use of this information.

Note that the content of the documents is protected by Canadian intellectual property legislation.

Chantal Dion
Chemical and Biological Hazards Prevention, IRSST

Guy Perrault
Consultant

Mounia Rhazi
Institut Armand-Frappier



This publication is available free of charge on the Web site.

This study was financed by the IRSST. The conclusions and recommendations are those of the authors.
This publication has been translated; only the original version (R-724) is authoritative.

IN CONFORMITY WITH THE IRSST'S POLICIES

The results of the research work published
in this document have been peer-reviewed.

ACKNOWLEDGEMENTS

The authors would like to thank André Dufresne, from the Université de Montréal, for his important contribution to the development of the design of the study and for relevant discussions and comments throughout the project. Our thanks also go to librarians Jacques Blain and Maryse Gagnon at the Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST) for their contribution to the literature search, as well as to secretaries France C. Lafontaine and Diane Laprés for their assistance in the layout of this document. In addition, we thank Helen Fleischauer for the translation of the document.

We also want to highlight the financial contribution of the *Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail* (ANSES, France) and to thank the experts in the “Tremolitic talc” working group for constructive discussions and comments in the finalization of this report.

SUMMARY

Talc is widely used in different workplaces, mainly in the ceramics, paint (antirust paint), gypsum joint compound, cosmetics, plastics and rubber industries. Since some talcs can contain amphiboles, namely tremolite, possibly with asbestiform (or fibrous) and non-asbestiform (cleavage fragments) morphology, it is important to know the origin and composition of the talcs to be able to implement exposure monitoring strategies and means of prevention appropriate for workers and other users.

Several definitions and applications of the term asbestos are used to classify amphiboles, whether it is in studies on health effects, in exposure monitoring, or for regulatory purposes. Considering the different opinions and contradictory studies regarding definitions, analytical methods, regulations, and the health effects of non-asbestiform tremolite, the CSST (Québec workers' compensation board) asked the IRSST to carry out a literature review on tremolite, present in talc and vermiculite, in order to clarify the impacts on worker health and safety and to facilitate the implementation of means of prevention in the Québec context. This report covers the synthesis of the results obtained for tremolite in talc. Vermiculite and its components will be the subject of another study.

The primary objective of this study is to produce a review and a synthesis of the knowledge on tremolitic talc in relation to the different morphologies, asbestiform (asbestos) and non-asbestiform (cleavage fragments), and in relation to the following parameters:

- Metrology (definitions, characterization of the materials, sampling and exposure);
- Regulations (standards and regulatory criteria applied in the different countries);
- Epidemiological data on the health effects.

Since the early 1990s, numerous studies have focused on the elongate mineral particles (EMPs) generated from the milling and fracturing of non-asbestiform amphibole minerals, defined as cleavage fragments. More particularly, the studies have focused on tremolite, occurring naturally in certain talc and vermiculite deposits, ores that are used in different consumer products. However, information is still limited on the exposures and health effects of these EMPs.

Experts, analysts, researchers and government scientists have not reached a consensus on the definition or differentiation of asbestiform and non-asbestiform amphiboles (cleavage fragments). While the distinction between cleavage fragments and fibres is theoretically clear, it is rather obscure from the analytical standpoint. With the use of complementary analytical methods such as phase contrast microscopy, scanning electron microscopy, transmission electron microscopy with selected area electron diffraction (SAED), or analytical electron transmission microscopy (SAED coupled with energy dispersion X-ray spectrometry), it would be possible to confirm the presence of asbestos fibres in an ore or a material and, more specifically, to determine the concentration in the air of fibres, asbestiform tremolite fibres, cleavage fragments of tremolite and talc fibres, if there was a consensus on the differentiation criteria to be used.

Most of the studies describing the health effects related to talc exposure contain very little information on the characterization of the talc involved. Even if the analytical methods

characterized the presence of amphiboles beyond any doubt, and quantified the asbestiform and non-asbestiform portions, it is rather unlikely that toxicology studies can be performed on completely pure products because talcs are generally a mixture of different minerals of variable concentration. However, this information would be invaluable in epidemiology for establishing better dose-response relationships.

Talc dust exposure is associated with respiratory disease such as NMRD (non-malignant respiratory disease), particularly pneumoconioses, and lung cancer, in the presence of other carcinogenic agents. In fact, talc ore dust can cause silicosis, talcosis, and mixed pneumoconiosis, but the causal share between talc, quartz and the other silicotic agents cannot be determined.

Millers do not present a significant increase in lung cancer risk, but miners could show significant tendencies or increases in risk in the presence of other carcinogens such as radon, quartz or asbestos. Use of the weighted concentration (dust or respirable dust) as exposure metric is a poor predictor of the fibre or elongate mineral particle concentration. The result is a possibly incorrect classification of cases, which complicates the establishment of a dose-response relationship.

The possibility of mesothelioma related to talc dust exposure remains a controversial subject. Mesotheliomas present diagnostic and causal recognition difficulties. With the current state of knowledge, there is no proof linking mesothelioma and exposure to talc not containing asbestos or asbestiform fibre.

From the results of epidemiological studies, it is difficult to answer definitively, with supporting proof, the question about the health risk of non-asbestiform tremolite (cleavage fragments), due to deficiencies in exposure characterization. In fact, no study had well characterized and well sampled cleavage fragment concentration results for the workers' breathing zones.

With all these uncertainties about exposures and health effects, research is still necessary in both toxicology and epidemiology as well as on exposure measurements, sampling, and on analytical methods. Furthermore, mineralogic studies of lung tissue (biometrology) could identify abnormal burdens and characterize the fibres and EMPs. These studies could help in defining the analytical and sampling methods that will more suitably measure the relevant toxicity characteristics. The results should also contribute to the development of recommendations for worker protection.

TABLE OF CONTENTS

1. INTRODUCTION.....	1
2. CONTEXT	3
3. OBJECTIVES.....	5
4. METHODOLOGY.....	7
5. METROLOGY (DEFINITIONS AND ANALYSES).....	9
5.1 Definitions and terminology	9
5.1.1 Asbestos	9
5.1.2 Asbestiform	10
5.1.3 Non-asbestiform (and cleavage fragments).....	10
5.1.4 Tremolite	11
5.1.5 Talc.....	12
5.1.6 Other definitions.....	15
5.2 Characterization and analysis.....	18
5.2.1 Sampling and analysis.....	18
5.2.2 Reference methods	19
5.2.3 Occupational exposure to talc dust.....	22
6. REGULATIONS AND RECOMMENDATIONS (ASBESTOS AND TALC).....	25
6.1 Standards and recommendations	25
6.2 History of the United States regulations	27
7. EPIDEMIOLOGICAL STUDIES	29
7.1 Reviews.....	29

7.2	Scientific articles.....	29
7.3	Other publications.....	30
7.4	Articles not retained for the epidemiology section.....	30
7.5	Summary of the results of epidemiological studies	31
8.	DISCUSSION AND CONCLUSION	33
8.1	Definitions and metrology (characterization and regulations)	33
8.2	Epidemiological studies.....	34
8.2.1	NMRD.....	34
8.2.2	Lung cancer	34
8.2.3	Mesothelioma	35
8.2.4	Limitations of the interpretations of the epidemiological studies	35
9.	RECOMMENDATIONS	37
10.	BIBLIOGRAPHY	39
	APPENDIX A: SYNONYMS AND COMMERCIAL NAMES OF TALC	46
	APPENDIX B: EPIDEMIOLOGICAL STUDIES	47
	Appendix B1. Reviews.....	48
B1.1	ATS (1990).....	48
B1.2	Baan (2007) and IARC (2010)	51
B1.3	Wild (2006).....	55
	Appendix B2. Scientific articles	61
B2.1	Gibbs et al. (1992)	61
B2.2	Gamble (1993).....	61
B2.3	Hull et al. (2002).....	62
B2.4	Roggli et al. (2002).....	62

B2.5 Honda et al. (2002)	63
B2.6 Ramanakumar et al. (2008)	64
B2.7 Wild et al. (2008)	66
Appendix B3. Other publications	68
B3.1 OSHA (1992)	68
B3.2 Guthrie (1992)	68
B3.3 Ilgren (2004)	68
B3.4 Gamble and Gibbs (2008)	69
B3.5 Price (2010)	72
APPENDIX C: TABLES TAKEN FROM WILD <i>ET AL.</i> (2006)	73
APPENDIX D: ADAPTED IARC TABLES (2010)	77

LIST OF TABLES

Table 1: Asbestiform and non-asbestiform varieties of selected silicate minerals, chemical composition and CAS # ¹	9
Table 2: Mineralogic composition of some European and American talcs	16
Table 3: Occupational exposure levels for talc	23
Table 4: Occupational exposure limits (OELs) – talc and asbestos ¹	26
Table B1: Analytical grid – Reviews – ATS 1990 - Workers	50
Table B2: Analytical grid – Reviews – Baan (2007) and IARC (2010)	54
Table B3: Analytical grid – Reviews – Lung cancer Wild (2006).....	59
Table B4: Analytical grid – Articles – Gibbs <i>et al</i> (1992)	61
Table B5: Analytical grid – Articles – Gamble (1993)	62
Table B6: Analytical grid – Articles – Hull <i>et al.</i> (2002)	62
Table B7: Analytical grid – Articles – Roggli <i>et al.</i> (2002).....	63
Table B8: Analytical grid – Articles – Honda (2002).....	64
Table B9: Analytical grid – tremolitic talc – Ramanakumar <i>et al.</i> (2008).....	65
Table B10: Prevalence of lifetime exposure to talc	65
Table B11: Odds ratios (OR) for lung cancer following talc exposure	66
Table B12: Analytical grid – Articles – Wild <i>et al.</i> (2008).....	67
Table B13: Summary of results for lung cancer and mesothelioma from studies of NY talc workers	70
Table C1: Summary characteristics of talc exposed populations in talc producing companies ...	74
Table C2: Summary characteristics of talc exposed populations in other industries	75
Table C3: Lung cancer and mortality from all causes in the talc producing companies	75
Table C4: Lung cancer relative risks in relation to talc exposure in other industries	76

Table D1: Cohort studies of mortality from and incidence of lung cancer in populations occupationally exposed to non-asbestiform talc 78

Table D2: Cohort studies of mortality from and incidence of lung cancer in workers occupationally exposed to non-asbestiform talc in user industries 84

LIST OF FIGURES

Figure 1: Lung cancer and mesothelioma mortality in workers in New York State and Norway.....	72
--	----

1. INTRODUCTION

Asbestos, represented by six commercially exploited mineral species, is one of the products that have been most extensively studied worldwide, and its effects on worker health are well known. The scientific literature discusses elongate mineral particles (EMPs) which have also been exploited commercially (wollastonite, attapulgite and sepiolite) or that can occur naturally in other minerals (talc, vermiculite and taconite) but are not considered as asbestos. Since the early 1990s, several studies have focused on the EMPs generated from the milling and fracturing of non-asbestiform amphibole minerals, often defined as cleavage fragments. More particularly, the EMPs of tremolite, a mineral occurring naturally in some talc and vermiculite deposits, are used in different consumer products. However, information on the exposures and health effects of these EMPs is still limited (NIOSH, 2011).

Talc is widely used in different workplaces, mainly in the ceramics, paint (antirust paint), gypsum joint compound, cosmetics, plastics and rubber industries, etc. Since some talcs can contain tremolite, it is important to know their origin and composition in order to implement suitable exposure monitoring strategies and means of prevention for workers and other users.

Several terminologies are used to classify amphiboles, to which tremolite belongs, by their asbestiform and non-asbestiform names. The scientific literature contains several definitions and applications of the term asbestos related to dimensions, characteristics, mineralogy, etc., whether in studies on health effects, in exposure monitoring, or for regulatory purposes. Discussion continues between specialists from various disciplines at many levels: legislation, the geological or mineralogic sciences, the mining industry, the medical sciences (hygienists, physicians and toxicologists), risk management and others. Considering the different contradictory opinions and studies about the definitions, analytical methods, regulations, and on the health effects of non-asbestiform tremolite, the CSST (Québec workers' compensation board) asked the IRSST to carry out a literature review on tremolite, present in talc and vermiculite, in order to clarify the impacts on workers' health and safety and to facilitate the implementation of means of prevention in the Québec context. For its part, ANSES¹ (previously AFSSET²) asked the IRSST to produce a literature synthesis more specifically focused on tremolitic talc.

This research report presents the synthesis of the results obtained for tremolite present in talc.

¹ Agence nationale de sécurité sanitaire, de l'alimentation, de l'environnement du travail (France)

² AFSSET: Agence française de sécurité sanitaire de l'environnement et du travail (France)

2. CONTEXT

The American Thoracic Society (ATS), Occupational Safety and Health Administration (OSHA) and National Institute for Occupational Safety and Health (NIOSH) examined the evidence of health effects of non-asbestiform tremolite around the 1990s.

The ATS created a committee in 1988 to document the health effects of tremolite, from the standpoint of epidemiology and animal studies, mineralogy and regulations. The objective was to render a decision on the mineralogic distinction between an asbestiform fibre (AF) and a cleavage fragment (CF) and the impact of this distinction on biological activity (ATS, 1990). Due to a lack of consensus between mineralogists and the limited information on published data about the species (AF or CF) used or observed in animal and humans studies, the ATS decided to ignore the distinction between the two morphologies and to instead consider fibres of different sizes. It was then impossible to come to a conclusion about the biological effects based on the CF and AF distinction. The ATS, invoking the precautionary principle, proposed to regulate it as a result, and to implement the same prevention measures with asbestiform and non-asbestiform fibres (cleavage fragments) of the same sizes. Recommendations were issued for continuing more extensive research on the biological consequences of each of the known mineralogic distinctions and on the possibility of modifying the concept of “regulated fibre” (length/diameter ratio greater than 3:1; length greater than 5 µm) to better reflect the biological effects.

In 1986, OSHA issued two standards for asbestos exposure, in industry in general, and in the construction sector. They contained the definitions of the six varieties of asbestos and actinolite, tremolite and anthophyllite (ATA) were recognized as existing in the asbestiform and non-asbestiform forms. While OSHA recognized a mineralogic distinction between the two forms, they were regulated in the same way, namely as exposure to “true asbestos.” Controversy then arose, and delayed the adoption of regulations until 1990.

Historically, OSHA asbestos exposure is measured by considering fibres longer than 5 µm and whose length/diameter ratio (aspect ratio) is greater than 3:1, by using phase contrast microscopy (PCM). Such aspect ratio, as used by OSHA (and supported by the ACGIH and NIOSH), would differentiate fibres from particles in an air sample. However, this statement is not a universally accepted mineralogic criterion.

Mineralogists consider a mineral fibre as a crystalline unit that grows individually into an elongate form. Cleavage fragments are produced by crystal fracture, parallel to their sides. CFs of ATAs can resemble fibres and meet OSHA’s definitions of a fibre. These CFs, also defined by terms such as “elongate, acicular, fibrous,” are not considered as “true” asbestos fibres by many mineralogists. OSHA agrees with the fact that the mineralogic terminology identifies distinct and different mineral formations. However, at the microscopic level, as observed with air samples, this difference is not as clear. For the data on health effects, OSHA mentions that it is impossible to clearly differentiate between exposures to asbestiform minerals and exposures to non-asbestiform minerals, since they generally coexist as a mixture (OSHA, 1992).

In 1990, OSHA proposed withdrawing its previous regulations and not issuing regulations on non-asbestiform ATAs in the same way as asbestos. OSHA concluded that there is insufficient evidence that the non-asbestiform form of tremolite, actinolite and anthophyllite will produce adverse health effects, of the same type and severity as those produced by chronic exposure to amphibole asbestos.

The two organizations therefore realized that the scientific evidence was insufficient to arrive at a conclusion about the presence or absence of health effects, but that the effects noted with non-asbestiform tremolite seemed less severe than those caused by asbestiform tremolite. Furthermore, OSHA extended these concepts to other amphiboles (anthophyllite and actinolite). The ATS, by invoking the precautionary principle, proposed applying the same preventive measures with asbestiform and non-asbestiform fibres, whereas OSHA decided to no longer regulate non-asbestiform fibres due to a lack of evidence about their toxicity.

At the same time, the National Institute for Occupational Safety and Health (NIOSH, 1990) revised its recommendation regarding occupational exposure to asbestos fibres. Due to concerns about the potential health risks associated with worker exposure to EMPs of mineralogic composition similar to asbestos fibres, and the incapacity of the routine analytical method (phase contrast microscopy, PCM) to differentiate individual EMP particles from asbestos fibres, NIOSH, as a precautionary measure, defined airborne asbestos fibres to include not only fibres of the six asbestos minerals but also EMPs originating from their non-asbestiform analogue. NIOSH retained the use of PCM for measuring airborne fibre concentrations and for counting EMPs longer than 5 µm and with an aspect ratio of 3:1 or more. Since then, concerns and discussions have arisen about this recommendation at NIOSH and are presented in a recent document (NIOSH, 2011), namely:

- “NIOSH’s explicit inclusion of EMPs from non-asbestiform amphiboles in its 1990 revised definition of airborne asbestos fibers is based on inconclusive science and contrasts with the regulatory approach subsequently taken by OSHA and by MSHA.
- The revised definition of airborne asbestos fibers does not explicitly encompass EMPs from asbestiform amphiboles that formerly had been mineralogically defined as tremolite (e.g., winchite and richterite) or other asbestiform minerals that are known to be (e.g., erionite and fluoro-edenite) or may be (e.g., some forms of talc) associated with health effects similar to those caused by asbestos.
- The specified dimensional criteria (length and aspect ratio) for EMPs covered by the revised definition of airborne asbestos fibers may not be optimal for protecting the health of exposed workers because they are not based solely on health concerns.
- Other physicochemical parameters, such as durability and surface activity, may be important toxicological parameters but are not reflected in the revised definition of airborne asbestos fibers.
- NIOSH’s use of the term “airborne asbestos fibers” to describe all airborne EMPs covered by the REL differs from the way mineralogists use the term and this inconsistency leads to confusion about the toxicity of EMPs.”

3. OBJECTIVES

The primary objective of this study is to produce a review and synthesis of the knowledge on tremolitic talc in relation to the different morphologies, asbestiform or non-asbestiform (cleavage fragments), and in relation to the following parameters:

- Metrology (definitions, characterization of materials, sampling and exposure);
- Regulations (standards and regulatory criteria applied in the different countries);
- Epidemiological data on the health effects.

4. METHODOLOGY

The literature search was done first, from the 1990s to 2005, in the following bibliographical sources: Chemical Abstracts, Medline/PubMed, Toxline, CISDOC (International Labour Office), INRS, NIOSHTIC Biblio, Scirus, BIOSIS, BIOME, CANADIANA, HSELINE and CSST (ISST). The key words used, in French and in English, covered the following subjects: actinolite, asbestos, amphibole, anthophyllite, asbestiform, attapulgitite, non-asbestiform, palygorskite, richterite, talc, tremolite, vermiculite, winchite, wollastonite and zonolite; with characterization, hazard, effect, epidemiology, exposure, identification, impact, inhalation, exposure measurements, dusts, health, safety, sensitization and toxicology. Two literature search updates were done in November 2009 and April 2010, based on the same criteria (bibliographical sources and key words).

To ensure the quality and accessibility of this knowledge, the articles retained come from peer-reviewed scientific journals, reports from recognized large-scale scientific international and governmental organizations, from institutional databases or university theses. The reasons for excluding articles were: case histories, methodological limitations, inaccessibility, language (other than French and English), general documents on asbestos, environmental studies and articles dealing with the therapeutic and perineal use of talc, other minerals (vermiculite, sepiolite, wollastonite, attapulgitite, erionite, etc.) as well as toxicological, animal or mechanistic studies.

In total, close to 1325 publications, published after 1990, were identified by our literature searches. After an initial review, approximately 550 data were eliminated because they were duplicates. Publications that were not in English or French (14) were then eliminated. Of the 760 remaining data, more than 650 were excluded for their non-relevance to the subject or for the reasons mentioned above. In the end, 90 documents were retained, of which only 34 have been cited in the present bibliography. According to scientific usage, the references that are cited in recent articles or reports are not repeated, unless they are used specifically in the text.

Starting from the ATS and OSHA documents, the scientific and technical literature search made it possible to determine the presence or absence of new data on the evaluation of the toxicity and health risk of amphibole fibres, mainly asbestiform and non-asbestiform tremolite, and any other natural mineral fibre or ores that could be contaminated by tremolite or have the same dimensional characteristics as tremolite. A less formal literature search was also done to collect the information tools or technical documents that were developed by governmental and private organizations worldwide, to promote the identification and knowledge of these different entities and to recommend means of control.

The selected articles were compiled in the Reference Manager database and were grouped in three sections: metrology (including definitions), regulations, and epidemiology. The articles in the metrology and regulation sections were examined and rigorously evaluated according to their scientific content. Articles on health effects in the epidemiology section were interpreted according to the most detailed criteria. In fact, a single study may not give definitive proof, whereas several studies may lead to contradictory conclusions. It is therefore important to carry

out a systematic general literature review according to criteria and rules, such as those described in the guidelines of Cochrane.³ High (H), intermediate (I), low (L) and absent (Ab) levels of evidence were used to compare the quality of the cited studies and to determine whether the lack of bias (in particular, related to knowledge about exposure) is such that the results can be considered reliable.⁴

The level of evidence is an interpretation by the authors of this report of the level of evidence determined by the review or the article consulted. To build on this interpretation, the report uses the following criteria:

- low: without adjustment for confounding factors and without dose-response relationship;
- intermediate: either one of its two conditions is missing;
- high: both criteria are met.

However, the interpretation can be modulated by the remarks or explanations in the text, most often in the discussion or in the conclusion. For example, the author of the consulted article or review may argue convincingly that the possibility of an adjustment for a confounding factor is not a determining factor.

To simplify the presentation, the health effects were grouped according to the following terminology:

- A: non-malignant respiratory diseases (NMRD) : pleural plaques, interstitial anomalies, chronic bronchitis, etc.;
- P: pneumoconiosis (silicosis, asbestosis, mixed pneumoconiosis, etc.);
- M: mesothelioma, described according to their number;
- C: lung cancer.

Section 5 of the report will discuss metrology, in terms of definitions and terminology, for asbestos, asbestiform and non-asbestiform morphologies, tremolite and talc, as well as the characterization, talc sampling and analytical methods, and occupational exposure to talc dust. Regulations and recommendations for asbestos and talc are discussed in section 6. The health effects are deduced from epidemiological studies and are summarized in section 7. The analysis grids from scientific reviews and articles are presented in Appendix B. A detailed description of the epidemiological data from the different articles can be consulted in Appendix C, in Tables C1 to C4 (taken from Wild, 2006) and in Appendix D, in Tables D1 and D2 (taken from IARC, 2010).

³ M.W. van Tulder, W. J.J. Assendelft, B.W. Koes, L.M. Bouter, and the Editorial board of the Cochrane Collaboration Back Review Group. Method Guidelines for Systematic Reviews in the *Cochrane Collaboration* Back Review Group for Spinal Disorders.

⁴ C. Lessard. Atelier méthodologique. La production et l'utilisation de méta-analyses et de revues systématiques de la littérature. Élaboration d'une revue systématique et d'une méta-analyse. 8^{es} journées annuelles de santé publique. Montréal. November 29 to December 2, 2004.

5. METROLOGY (DEFINITIONS AND ANALYSES)

5.1 Definitions and terminology

5.1.1 Asbestos

Asbestos is a commercial term that describes six natural minerals, hydrated silicates, divided into two groups: serpentine and amphiboles. Asbestos occurs in the fibrous form (asbestiform) and different properties give it its commercial value: low electrical and thermal conductivity, chemical stability, durability, high tensile strength, flexibility, etc. Most of the data on health risks involve the terminology of commercial minerals. However, there is confusion associated with the nomenclature and with the definitions of asbestos, which are not always uniformly applied (USGS, 2002; Meeker *et al.*, 2003). In fact, “asbestos” terminology varies greatly depending on its use by mineralogists, occupational hygienists and physicians, epidemiologists, chemists or analysts, and regulatory organizations.

Numerous silicates can occur in two forms, asbestiform and non-asbestiform. Table 1 lists the six ores whose fibrous (asbestiform) variety is regulated under the term “asbestos” as well as their particulate or non-fibrous equivalent (non-asbestiform).

Table 1: Asbestiform and non-asbestiform varieties of selected silicate minerals, chemical composition and CAS #¹

Asbestiform varieties (CAS #) ¹	Chemical composition ²	Non-asbestiform varieties (CAS #) ¹
Serpentine group		
Chrysotile (12001-29-5)	3MgO.2SiO ₂ .2H ₂ O	Antigorite (12135-86-3)
Amphibole group		
Actinolite asbestos (77536-66-4)	2CaO.4MgO.FeO.8SiO ₂ .H ₂ O	Actinolite (13768-00-8)
Anthophyllite asbestos (77536-67-5)	7MgO.8SiO ₂ .H ₂ O	Anthophyllite (17068-78-9)
Tremolite asbestos (77536-68-6)	2CaO.5MgO.FeO.8SiO ₂ .H ₂ O	Tremolite (14567-73-8)
Amosite (grunerite) (12172-73-5)	11FeO.3MgO.8SiO ₂ .H ₂ O	Grunerite (14567-61-4)
Crocidolite (12001-28-4)	Na ₂ O.Fe ₂ O ₃ .FeO.8SiO ₂ .H ₂ O	Riebeckite (17787-87-0)

¹: CAS (Chemical Abstract Service);

²: According to Kirk Othmer (1978).

In the amphibole group, the asbestiform and non-asbestiform forms of tremolite, actinolite and anthophyllite do not have a different name; this is why, in different regulatory texts, the term asbestos or asbestiform is added to the mineral's name. Each non-asbestiform mineral and its asbestiform equivalent have the same chemical composition, but differ in their crystalline growth.

5.1.2 Asbestiform

The term asbestiform refers to a morphology originating from the natural crystallization of a mineral into small crystals, into hair-like fibres (unidimensional). This morphology gives the mineral specific characteristics, including a high aspect ratio (length/diameter ratio), increased mechanical properties, flexibility and durability. In the asbestiform morphology, the crystals grew by forming long and filiform fibres. These fibres are found in bundles that can easily separate into smaller fibres (fibrils) which, during processes, retain their surface and activity properties. OSHA (1992) specifies that the asbestiform criterion does not depend on the crystalline structure but on how the crystal grows or its crystalline formation. When pressure is applied to an asbestos fibre, it will bend rather than break. The fibres can separate into fibrils of smaller diameter, often less than 0.5 μm . This effect refers to “polyfilamentous” terminology, which corresponds to the most important characteristic of asbestos (MSHA, 2005). The term asbestiform has not been defined for regulatory purposes. However, the EPA has a definition for the asbestiform morphology that is used to differentiate asbestiform minerals from cleavage fragments (EPA, 1993):

Said of a mineral that is like asbestos, i.e., crystallized with the habit of asbestos. Some asbestiform minerals may lack the properties which make asbestos commercially valuable, such as long fiber length and high tensile strength. With the light microscope, the asbestiform habit is generally recognized by the following characteristics:

- Mean aspect ratios ranging from 20:1 to 100:1 or higher for fibers longer than 5 μm . Aspect ratios should be determined for fibers, not bundles.
- Very thin fibrils, usually less than 0.5 micrometers in width, and
- Two or more of the following:
 - Parallel fibers occurring in bundles
 - Fiber bundles displaying splayed ends
 - Matted masses of individual fibers
 - Fibers showing curvature.

5.1.3 Non-asbestiform (and cleavage fragments)

For the most part, the non-asbestiform mineral varieties presented in Table 1 have had little commercial significance because they are less solid and less resistant. These varieties, with the same chemical formula as their asbestiform counterparts, do not develop unidimensionally into long fibres, but instead bi or three-dimensionally, resulting in a more massive morphology. When pressure is applied, non-asbestiform minerals fracture easily into prismatic particles, **cleavage fragments**, which result from the fracture or cleaving of the particles. Some particles are acicular (needle-like), and stair-step cleavage on the edges of some particles is common (Srebro, 1994). Particles of this morphology can, however, correspond to the definition of respirable fibre or WHO (World Health Organization) fibre when observed under a microscope (NIOSH, 2010). The difference is therefore in their crystallization process. In other words, cleavage fragments have the same chemical composition as the corresponding asbestos fibres, without having all the dimensional characteristics (length, diameter and aspect ratio), chemical and physical properties, or mechanical performance of asbestiform fibres.

In general, the asbestiform varieties of asbestos are characterized by long and thin fibres, while cleavage fragments of the corresponding non-asbestiform varieties consist of short fibres of larger diameter. A clear distinction between cleavage fragments and asbestos fibres would be that the width of the cleavage fragments is a function of the length, while the width of asbestos fibres is relatively constant, regardless of the length (Siegrist, 1980).

Cleavage fragments can form when non-fibrous (non-asbestiform) amphibole minerals are milled, for example in ore extraction and exploitation. Cleavage fragments are not asbestiform and are not included in the MSHA definition (2005). Within a population of non-asbestiform amphibole cleavage fragments, a fraction of particles may correspond to the definition of a fibre as adopted in different regulations. The dimensional distributions of asbestos fibres can be differentiated from those of cleavage fragments, but it may be difficult with a single particle to distinguish whether it is a cleavage fragment or an asbestos fibre (ATSDR, 2001; Meeker *et al.*, 2003).

In her testimony to OSHA during the revision of standards in 1986, Dr. Wylie indicated that: “A particle of any mineral which is formed by regular breakage is called a **cleavage fragment**. Mineralogically, a fiber or fibril is a crystal which has attained its shape through growth, in contrast to a cleavage fragment which has attained its shape through regular breakage. The shape of amphibole cleavage fragments is somewhat variable depending upon the history of the mineral sample. Some amphiboles when crushed will produce a population of particles which may have the average aspect ratio of 5 to 1 or 6 to 1, whereas other amphibole samples when crushed may produce a population of particles whose aspect ratios average closer to 8 to 1 or 10 to 1. And in almost any population of amphibole cleavage fragments, it is possible to find a few particles whose aspect ratios may extend up to 20 to 1 or perhaps even higher.” (OSHA, 1992).

5.1.4 Tremolite

Tremolite is a mineral species belonging to the amphibole group, a hydrated silicate of magnesium and calcium ($\text{Ca}_2\text{Mg}_5\text{Si}_8\text{O}_{22}(\text{OH})_2$). The molecular structure of amphiboles consists of two chains of SiO_4 molecules that are bound to the oxygen atoms. The chains are held together by cations (calcium, magnesium, iron, etc.). Two hydroxide groups are bound to the central cation and are completely contained in the structure, which consists of a stack of ribbons. The basic crystalline structure of all amphiboles is identical, but the chemical composition is different.

Tremolite can be found as a natural contaminant of the chrysotile form of asbestos, in some talc deposits (New York State) and vermiculite deposits (Libby Mine, Montana). Abundantly distributed at the earth's surface, tremolite has a very varied chemical composition, related to the variations in magnesium, iron, calcium and sodium content (Langer, 1991).

Tremolite can be present in the two types of morphologies, asbestiform and non-asbestiform. Non-asbestiform tremolite is the predominant form found in the earth's crust, while asbestiform tremolite is present almost everywhere in the world (including the states of Maryland and California) and in natural materials (Veblen and Wylie, 1993). Tremolite asbestos has rarely been found in commercially mined deposits in the United States. However, up until 1996, deposits of anthophyllite and tremolite asbestos were commercially mined, for use in cement, in the

Rajasthan region in India. Tremolite asbestos and other amphibole asbestos appear to be present in some commercial talc and vermiculite deposits (ATSDR, 2001).

5.1.5 Talc

The term “talc” generally refers to pure mineral talc, and to industrial mineral products marketed under the name “talc” that contain it as one of their main ingredients, in a proportion varying from 35% to close to 100% (IARC, 2010). Talc deposits consist of complex mixtures of mineral particles and can vary substantially in composition, depending on the deposit, and even within relatively close geographical zones (Zazenski, 1995). Industrial talcs vary greatly in their talc content and content of other minerals (IARC, 2010). A list of synonyms or commercial products including talc is presented in Appendix A.

Talc particles are mainly in the form of plates. More rarely, they can take the form of long and thin fibres (fibrous talc), in a bundle that can be easily separated (asbestiform talc). Asbestiform talc must not be confused with talc containing asbestos (ACGIH, 2010).

5.1.5.1 Mineralogy

The chemical formula for talc (CAS No. 14807-96-6), also called soapstone, steatite and talcum powder, is quite stable and has little ion substitution within its mineral network: $\text{Mg}_3\text{Si}_4\text{O}_{10}(\text{OH})_2$. Talc is characterized by two dimensional structures in sheets, separated by weak forces (Van der Waals); it can be cut and is very soft, which gives it its characteristic greasy feel, useful for certain industrial applications. It is considered as a somewhat inert, hydrophobic and rather insoluble material in water.

Talc is formed by the alteration or metamorphism of existing rocks by fluids containing silicon and/or magnesium. The chemical composition of talc and the presence of associated minerals will depend on the original type of rock and the type of transformation. This is why it is often associated with other minerals: calcite, dolomite, magnesite, asbestiform and non-asbestiform amphiboles (tremolite and anthophyllite, quartz, pyrophyllite, micas, chlorites, and serpentines) antigorite, and much more rarely, chrysotile and lizardite. Talc derived from magnesian carbonate may contain quartz and little or no amphiboles. However, in deposits originating from rocks rich in siliceous dolomites or magnesium, amphiboles can be very abundant (30 to 70%), such as in Gouverneur in New York State (IARC, 2010).

5.1.5.2 Talc production and use

Talc is extracted in several countries and transformed in many manufacturing industries for use in various products. It is found in deposits almost everywhere in the world: in America (along the Appalachian chain, in California and in Texas), in Europe (Germany, Italy, Austria, Scotland), and in South Africa (Transvaal region) (ATSDR, 2001). In the United States in 2008, 8 talc mines (soapstone, steatite, talc) were operated in 5 states: Montana, New York, California, Texas and Vermont. The operations, in these open pit mines, contributed to 99% of national production. The five main US producers are, in decreasing order of production: Luzenac North America (member of the Luzenac Group), American Talc Co., Specialty Minerals Inc. (Barretts, MT), Gouverneur Talc Co. (subsidiary of R.T. Vanderbilt Co., Inc.), and Protech Minerals Inc. (Virta,

2009a). Early in 2008, Gouverneur Talc Co. permanently stopped talc extraction at its installations in Gouverneur, NY, in operation since 1948. The company operated from stocks for the remainder of the year to fill its clients' orders (Virta, 2009a).

World production of talc and pyrophyllite in 2008 was estimated at 7.51 million metric tons, whereas talc production in the United States was 545,000 metric tons. China was the primary producer of talc worldwide, followed by the United States, India, Finland and France (crude) (Virta, 2009a, 2009b). More than 36% of United States talc production has been exported.

The uses for talc are: ceramics (31%), paper (21%), paints (19%), roofing (8%), plastics (5%), rubber (4%), cosmetics (2%) and others (10%) (Virta, 2009b). Different grades are available on the market and have physical characteristics specific to certain applications. For example, for use in ceramics, the presence of manganese and iron is not desirable; for high frequency insulators, small quantities of impurities are tolerated: < 0.5% calcium oxide, 1.5% iron oxide, and 4% aluminum oxide. In the cosmetics and pharmaceutical field, talc must be grain-free, fine, chemically pure and with a "pleasant" colour (IARC, 1987 and 2010).

In the United States, commercial talcs are classified as cosmetic grade, which does not contain asbestos, and as industrial grade, which may contain asbestiform and non-asbestiform particles, depending on the expected use. One important source of industrial quality talc extracted in New York State is called tremolitic talc, because it contains a significant amount of tremolite (ATSDR, 2001).

Talc products containing more than 95% mineral talc are used in cosmetics, baby powder, pharmaceuticals, ceramics, paper and rubber. Relatively pure talc is used in cosmetics (more than 98% talc) and in pharmaceuticals (more than 99% talc). Talcum powder is cosmetic grade (Zazenski, 1995; IARC, 2010). However, the comparison of regulations or uses in different countries is difficult due to the heterogeneity of definitions and classifications of "medications" and "cosmetics" (Risk & Policy Analysts Limited, 2004).

The Food Chemical Codex provides specifications for food grade talc. A guide on a voluntary basis was initiated in 1976 by the cosmetics industry, toiletry products industry, Fragrance Association, the United States Pharmacopeia, and by Food Chemical Codex which establishes quality assurance specifications for talcs to ensure the purity of their products (Zazenski, 1995; IARC, 2010).

5.1.5.3 Composition of talcs

Table 2 summarizes the composition of different European and American talcs, as reported by different authors and in IARC monographs (1987, 2010).

One study carried out on several bulk British talc samples showed a very variable composition in mineral talc content. The major identified contaminants of talc are chlorite, carbonates and quartz (generally < 2%, except for one talc: > 5%). Tremolite fibres were found in three samples, in a major phase in one of them. There were no other varieties of asbestos. In fact, there is only one source of talc in the British Isles (Shetland), which produces a small portion of the market. The

majority of the talcs used in Great Britain are therefore imported as powder or crushed or milled rock, depending on needs. At the time of the study, they originated from: Norway, France, Italy, China, India, Belgium, the United States, etc. (Pooley and Rowlands, 1977).

An investigation on cosmetic talcum powders from the Italian and international markets by electron microscopy, electron diffraction, and energy-dispersive X-ray analysis, showed that asbestos was detected in 6 of the 14 talc samples originating from the European pharmacopeia (Paoletti *et al.*, 1984). Chrysotile alone was identified in 3 samples, tremolite asbestos and anthophyllite asbestos were found in 2 samples, and chrysotile and tremolite asbestos were identified in one sample. The authors noted that in all the talcum powders analyzed, fibrous talc particles were often present, morphologically similar to amphibole asbestos fibres. Taking into account the fibres with an aspect ratio $> 3:1$ and diameter $< 3 \mu\text{m}$, the percentages of asbestos fibres varied from < 0.03 to 0.13% for 4 samples, and from 18 to 22% for the two other samples (ATSDR, 2001).

A study by Rohl *et al.* in 1976 (cited in IARC, 2010) examined 20 baby powders and facial talcum powders and one pharmaceutical talc, purchased in retail stores in New York between 1971 and 1975. The concentrations of tremolite, anthophyllite, quartz and other minerals were estimated by X-ray diffraction, PCM and TEM. One sample out of the 21 consisted totally of corn starch, and one other contained pyrophyllite and a small amount of talc. Quartz was found in 9 samples, tremolite was reported in 9 samples, anthophyllite was found in 7 samples, and chrysotile was identified in two samples.

A study by Jehan, reported by IARC (2010), was carried out on cosmetic talcs (body talcum powder and baby powder). Analysis of 60 samples by different techniques identified the presence of asbestiform and non-asbestiform chrysotile, tremolite and anthophyllite, as well as quartz. These talcs were used in Pakistan between 2000 and 2004 (IARC, 2010).

5.1.5.4 Gouverneur Talc in New York State

Industrial talc mined in New York State, also known as Gouverneur talc or tremolitic talc, contains fibrous varieties of talc, tremolite and anthophyllite (Van Gosen, 2007). A NIOSH occupational hygiene assessment in 1980 reported that the dust of New York talc from the R.T. Vanderbilt (RTV) mine contained asbestos (chrysotile, tremolite and anthophyllite) or non-asbestiform analogues (NIOSH, 2011). These data were the subject of debates on the presence of fibrous amphiboles meeting the definition of asbestos fibres but also “transition fibres” partially consisting of talc and anthophyllite.

The scientific literature indicates that these talc deposits and their industrial products may contain asbestos (ATS, 1990; NTP 1993). In 1992, OSHA noted that the discussion surrounding the mineralogic content of New York talc was inconclusive, but that the presence of asbestiform talc in the ore may have led to the identification of asbestiform tremolite and anthophyllite. One OSHA report suggests that cleavage fragments of non-asbestiform tremolite and anthophyllite in the talc ore and products may have been incorrectly identified as asbestos. New York talc ore may be composed of non-asbestiform tremolite, non-asbestiform anthophyllite, massive and asbestiform talc, and small quantities of other ores (ATSDR, 2001). Particles with a different mineralogic definition, other than asbestiform and non-asbestiform ores, were also identified.

These are the “intermediate” or “transition” fibres, which are between anthophyllite and talc and have a morphology more similar to asbestos, with aspect ratios > 20:1 and even up to 100:1 (OSHA, 1992).

In the framework of a NIOSH industrial hygiene assessment conducted in RTV mines, the analyses of the talc samples by means of X-ray diffraction and petrographic microscope showed that they contained from 4.5–15% anthophyllite (with some particles being classified as asbestos). However, a document prepared by Kelse in 2005 instead reported 1–5% non-asbestiform anthophyllite (NIOSH, 2011).

Air samples collected by NIOSH (1980) at the mine and in the mill were analyzed by transmission electron microscopy (TEM): 65% of the EMPs > 5 µm were anthophyllite, and 7% were tremolite (a large part was non-fibrous tremolite).

Serpentine and amphibole minerals generally develop from the alteration of other minerals. As a result, they can exist in the form of partially altered minerals presenting variations in their elementary compositions, often called “transition minerals.” Thus, the elementary composition of individual mineral particles may vary in a mineral deposit containing transition minerals, which could explain the differences noted in the composition of the talc from the RTV mine (NIOSH, 2011).

5.1.6 Other definitions

NIOSH (2011), at the end of its *Current Intelligence Bulletin 62*, gives definitions of general mineralogic terms and specific minerals originating from different sources.

Table 2: Mineralogic composition of some European and American talcs

Identification and location	Composition and morphology	Analytical methods	Reference
Talc from Italy (Val Chisone) Grade 00000	Small amounts of tremolite fibres (a few samples only) and silica, but also quartz, muscovite, chlorite, garnet, calcite, magnesite. 92% talc; 3% chlorite; 1% carbonate and < 1% quartz. No tremolite asbestos or chrysotile. Tremolite.		Rubino (1976) cited in EPA (1992) and IARC (1987, 2010) Wagner (1977) Cited in IARC (1987) EPA (1992) and IARC (1987)
Cosmetic talcs from Italy and from international markets	Asbestos detected in 6/14 talcs from the European pharmacopeia (<0.3 to 22%): chrysotile (3 samples); tremolite and anthophyllite (2 samples, up to 20%); chrysotile and tremolite (1 sample). Particles of fibrous talc, morphology similar to amphibole fibres were identified.	EM, EDAX and SAED Aspect ratio: >3:1 Diameter < 3 µm	Paoletti (1984) Cited in ATSDR (2001)
Talc from Austria (3 mines, Styrian Alps)	(1) Talc-chlorite mixture (0.5 – 4% quartz); (2) Talc-dolomite mixture (25% talc and <1% quartz); (3) Mixture of equal proportions of quartz, chlorite and mica.		Wild (2002)
Talc from France (Pyrénées)	Mixture of talc chlorite with quartz contamination < 3%.		Wild (2002)
Luzenac talc, 15M00	90% talc, 8% chlorite, 1% dolomite. No asbestos.		IARC (1987)
Talc from Norway	Mainly talc and magnesite, and traces of quartz, tremolite and anthophyllite.		Wergeland (1990)

Identification and location	Composition and morphology	Analytical methods	Reference
Talcs from New York:	Composition differs significantly depending on location. Major fibrous component: tremolite and anthophyllite.	EM	Kleinfeld (1973) cited in IARC (1987) (Van Gosen, 2007)
St. Lawrence County (Gouverneur)	Fibrous varieties of talc, tremolite and anthophyllite.		
	Tremolitic talc: high proportion of tremolite and talc, transition talc/anthophyllite, antigorite, lizardite and quartz. Non-asbestiform amphiboles.	XRD and petrographic analyses	Gamble (2008) Skinner (1988) IARC (2010)
	14–48% talc, 37–59% tremolite (fibrous and non-fibrous), 4.5–15% anthophyllite (fibrous and non-fibrous); 0.25–2.6% quartz, <1% calcite and dolomite and 10–15% serpentines (lizardite and antigorite).		Dement (1980) cited in IARC (1987)
Nytaal 100	30–50% tremolite, 20–40% talc, 20–30% serpentine, 2–10%, anthophyllite and 0.14% quartz. Amphiboles and serpentine (cleavage fragments).		IARC (2010)
Smith-Tremolitic Talc IT-3X, Vanderbilt Co.	All amphiboles appear to be cleavage fragments (non-asbestiform): 50% tremolite, 10% antigorite, 35% talc (25% fibrous), 2–5% chlorite. Average length of particles: 8.5 µm; Diameters (2000x): < 1 µm = 20%; 1–2 µm = 36%; 2–4 µm = 32%; 4–6 µm = 8%; 6–8 µm = 2%; 10 µm = 2%; Length of tremolite: 1 µm to 40–50 µm; Fine fibrous talc (mixture of talc and amphibole rich in magnesium) with a high aspect ratio. Tremolite is in the form of cleavage fragments (non-asbestiform).		Several authors cited in Gamble (2008)
Talc from Vermont	Talc (rolled and elongated particles) and magnesite (20–100%), chlorite and dolomite (5–20%) and < 5%: dolomite, calcite, quartz (trace), biotite, ankerite, chromite, phlogopite and oligoclase. No asbestos.	XRD Analytical EM	Boundy (1979) Selevan (1979) Cited in IARC (1987, 2010) and EPA (1992)
Talc from Georgia	Talc (70%), dolomite (20–30%), tremolite (10%) and little or no crystalline silica.		EPA (1992) IARC (1987, 2010)
Talc from Montana	Talc and little chlorite, dolomite, calcite and quartz < 0.8%. No fibres.		
Talc from Texas	Fibrous tremolite and antigorite: diameter: 0.5–3 µm; length: 4–30 µm. Little or no amphibole.	TEM	Greife (1980) and Gamble (1982) cited by IARC (1987, 2010), EPA (1992)
Talc from North Carolina	Acicular cleavage fragments: L/D up to 100:1; some diameters < 0.1 µm.		

EM: Electron microscopy; Analytical EM: Electron microscopy combining EDAX and/or SAED; EDAX: Energy dispersive analysis of X-rays; SAED: Selected area electron diffraction; XRD: X-ray diffraction.

5.2 Characterization and analysis

Talc, since it is formed by the alteration or metamorphism of rocks, is often associated with other minerals, some of which are known for their biological activity (IARC, 1987). Characterization of the samples is therefore necessary to distinguish the different components of bulk materials and airborne dusts. Considering the discussions about the different toxicities of asbestos fibres and cleavage fragments, being able to differentiate these two morphologies would be desirable in order to consolidate the exposure data (NIOSH, 2011).

OSHA (1992) defines cleavage fragments as mineral particles formed during ore milling, characterized by relatively parallel sides and moderate aspect ratios (less than 20:1). “Most cleavage fragments of the asbestos minerals are easily distinguishable from true asbestos fibres.” “True” cleavage fragments would mostly have diameters larger than 1 µm. However, there are no clear written procedures in the different methods for identifying an individual fibre.

A fibre is generally defined as a particle with an aspect ratio of at least 3:1 and a minimum length of 5 µm. Such a definition does not allow the microscopist to distinguish asbestos fibres from non-asbestiform amphibole particles, since all elongate particles are taken into consideration in the analysis. Although asbestiform particles and non-asbestiform particles are generally well defined, the counting criteria developed in the analytical methods do not eliminate the non-asbestiform phase. The effect is to overestimate the fibre concentration for asbestos-exposed populations but also to bias the studies on the harmfulness of asbestos fibres in the same way as the harmfulness of cleavage fragments (Gamble and Gibbs, 2008). The current challenge in the optimal characterization of talc and tremolite is to differentiate non-asbestiform amphiboles from asbestiform amphiboles.

5.2.1 Sampling and analysis

The methods used prior to 1970 for sampling and analyzing airborne fibres mainly consisted of collecting dusts with an impinge (liquid medium) and counting particles by optical microscopy (mpccf: million particles per cubic foot). Subsequently, other techniques were added for analyzing air samples collected on a membrane, including gravimetric analysis (mg/m³), phase contrast microscopy (PCM, f/mL), scanning electron microscopy (SEM, f/mL) and transmission electron microscopy with selected area electron diffraction (SAED) (TEM, f/mL), or analytical transmission electron microscopy (ATEM: TEM coupled with energy dispersive analysis of X-rays (EDAX)). For bulk samples, semi-quantitative analysis by polarized light microscopy (PLM) and quantitative analysis using the X-ray diffraction (XRD) technique are widely used, particularly to identify the different crystalline minerals contained in talc (amphiboles, chrysotile, magnesite, quartz, etc.) with an analytical sensitivity of 1–2%. However, XRD cannot provide information about the morphology (Pooley and Rowlands, 1977).

The complementary use of these different methods in the analysis and characterization of bulk materials or air samples allows a more precise approach for identifying and estimating the concentrations of fibres in the air. Several parameters can thus be observed: size, morphology, elementary composition, crystalline structure, and surface composition (ATSDR, 2001; NIOSH, 2011).

Phase contrast microscopy (PCM) is widely used for counting fibres in workplace air. However, this technique has limitations in terms of resolution and speciation of fibres. The PCM method does not identify the nature of the fibres and is based only on dimensional criteria, such as all particles meeting the definition of a respirable fibre (WHO, 1998): length (L) $> 5\ \mu\text{m}$, diameter (d) $< 3\ \mu\text{m}$, and aspect ratio (L/d) $> 3:1$. Analytical electron microscopy (EDAX) and selected area electron diffraction (SAED) provide information on the morphology, structure, chemistry of an individual talc particle or the associated minerals (EPA, 1992). The minimum measurable diameter is $0.2\ \mu\text{m}$ by PCM and SEM. However, SEM allows the fibres to be analyzed chemically. On the other hand, since ATEM allows chemical analysis of the elements, it can identify fibres, even very fine ones (less than $0.01\ \mu\text{m}$), based on their morphological, crystallographic and chemical characteristics.

Fibres can be analyzed differently depending on the method, either optical or electronic, in relation to counting rules: by PCM, fibres $\geq 5\ \mu\text{m}$, and length:diameter ratio $> 3:1$; by TEM, fibres $\geq 0.5\ \mu\text{m}$ with an L/d ratio $\geq 5:1$. Some laboratories apply criteria identical to PCM by taking into account only equivalent optical fibres for TEM analysis. Most of the regulations, except for the United States, take into account the WHO definition of a fibre by adding the diameter criterion, namely $< 3\ \mu\text{m}$. For asbestos fibre detection in bulk materials, particles $\geq 5\ \mu\text{m}$ with a length:diameter ratio $\geq 5:1$ are then taken into account. The different regulatory analytical methods for fibre counting do not distinguish between the asbestiform type and cleavage fragments. There are also differences in the definition of asbestiform morphology by optical or electronic methods, since the characteristics of asbestos vary at different magnifications (Millette and Bandli, 2005).

5.2.2 Reference methods

5.2.2.1 Sampling methods

Asbestos fibres and other mineral fibres are generally sampled on a membrane filter in a cowed cassette, according to the sampling and analytical methods described by most reference organizations including: WHO (1998), NIOSH 7400 (1994), IRSST 243 (1995), OSHA ID-160 (1998), MDHS 39/4 (HSE, 1995) and ISO 8672 (1993).

Two studies examined the performance of thoracic samplers for EMPs (Jones *et al.*, 2005; Maynard, 2002). Thoracic samplers allow the sampling of suspended particles that meet the aerodynamic definition of thoracic size (width $\leq 3\ \mu\text{m}$), namely the EMPs considered as most pathogenic. The results of the studies showed that the sampling efficiency of some thoracic samplers is independent of the length of the EMPs, at least up to $60\ \mu\text{m}$, indicating that the sampling characteristics for an aerosol of elongate particles should not be different from those of an isometric aerosol. In the study of Jones *et al.* (2005), the relative capacity of the thoracic sampler to produce uniform distributions of elongate particles on the surface of the membrane was also tested. Two samplers seemed to meet the minimal selection bias criteria with respect to the length of the elongate particles and a uniform distribution on the filters. However, none of these samplers was tested under field conditions.

NIOSH is currently evaluating these two thoracic samplers and the traditional cowled sampler in three mining environments. The results of these studies show that each of the samplers gives fibre concentrations proportional to their fibre burden rates (Lee *et al.*, 2008 and 2010). However, these thoracic samplers cannot be recommended until the impact of these results on the risk analysis has been evaluated (NIOSH, 2011).

5.2.2.2 Analytical methods

To apply the regulations in effect in different countries for fibres, routine workplace monitoring is supported by reference PCM methods, including: XP X43-269 (2002), ISO 8672 (1993), WHO (1998); NIOSH 7400 A criteria (1994a); HSE - MDHS 39/4 (1995); IRSST 243 (1995).

To measure environmental exposures to fibres or for specific cases or for research purposes, reference methods in analytical transmission electron microscopy (ATEM) have been validated and are recognized by different regulations: ISO 10312 (1995); ISO 13794 (1999); NFX 43-050 (1996), NIOSH 7402 (1994b), ASTM 6281-04 (2004); ASTM D5755-02 (2002a); ASTM D5756-02 (2002b), ASTM 6480-99 (1999) and the EPA (2003). ATEM is more rarely used due to the high cost and complexity of the instrumentation. Scanning electron microscopy (SEM) is used, particularly in Germany, ISO 14966 (2002) and VDI-3492 (2004) (AFSSET 2009).

To characterize fibres in bulk dusts, deposited dusts, materials or products, methods involving ATEM (similar to air measurements) or polarized light microscopy (PLM) can be used. Several reference methods by PLM are available, including EPA-600/R-93/116 (1993), IRSST 244 (1999), NIOSH 9002 (1994b), OSHA ID-191 (1992) and MDHS 77 (1994). PLM allows fibre identification through different optical properties, but the limit of detection requires a rather large particle size for the fibres. With ATEM, very fine fibres ($< 0.01 \mu\text{m}$) can be seen and the fibres specifically identified.

5.2.2.3 Differential analytical methods

Several studies have been published for the purpose of proposing counting criteria, generally by PCM, in order to distinguish between asbestiform and non-asbestiform amphiboles. However, the lack of reliable data and validated analytical methods, which can distinguish individual fibres, is a major limitation in the application of the definitions of airborne asbestos fibres.

In an appendix to the OSHA standard, a “differential counting” technique has been suggested as an approach for differentiating asbestiform from non-asbestiform EMPs. However, it specifies that the application of this differential counting technique requires “a great deal of experience” and is “discouraged unless it is legally necessary.” In this technique, EMPs considered as non-asbestiform by the microscopist are not counted; all EMPs whose morphology is not clear must be counted as asbestos fibres. An additional source of variability is thus added by the effect of this differential reading. This technique has not been formally validated and has not been recommended by NIOSH.

To count asbestos fibres in mines and quarries, the ASTM has proposed “discriminatory counting” integrating differential counting criteria. The method uses PCM and TEM sequentially. Air samples are first analyzed by PCM. If the initial fibre concentration exceeds the permissible

exposure limit (PEL), TEM is performed to determine the equivalent optical concentration only for regulated asbestos fibres. If the initial concentration of PCM fibres is between 0.5 and one time the PEV, “discriminatory counting” is then performed. “Discriminatory counting” is limited to fibre bundles, to fibres longer than 10 µm, and to fibres with a diameter less than 1 µm. If the number of “discriminatory” fibres is 50% or more of the initial number of PCM fibres, TEM is performed to determine an equivalent number of regulated PCM asbestos fibres only. These results are then compared to the regulatory limits (ASTM, 2006).

Harper *et al.* (2008) have also proposed an alternative method, by making a distinction based on the diameter of the particles and on the hypothesis that a good proportion of the cleavage fragments would have a diameter greater than 1 µm. The diameter of airborne cleavage fragments is greater than the diameter of asbestos fibres, even though an overlap is possible in the case of very fine cleavage fragments or thick fibrillar bundles. Since the difference in lengths is not so big, the overlap between the morphologies is greater. However, a clear distinction between cleavage fragments and asbestos fibres would be that the diameter of cleavage fragments is a function of their length, while the diameter of asbestos fibres is relatively constant, regardless of their length. Harper proceeded with the ASTM D7200-06 method, which already includes a procedure to determine whether the particles observed by PCM correspond to asbestiform fibres or to cleavage fragments. The ASTM method consists of three classes of particles:

- Class 1, potentially asbestiform, regardless of the dimensions: particles meeting the definition of a fibre according to NIOSH (length > 5 µm and aspect ratio > 3:1) as well as: curvature, split ends or bundles of fibrils;
- Class 2, potentially asbestiform fibres: particles meeting the definition of a fibre according to NIOSH and also length > 10 µm or diameter < 1 µm;
- Class 3, which corresponds to all other particles meeting the definition of a fibre according to NIOSH, including possible cleavage fragments.

The asbestiform fibre population is the sum of classes 1 and 2. The results show that the method could be suggested, but only after revalidation and the training of analysts (NIOSH, 2011). By using an additional criterion for class 2 (length > 10 µm and diameter < 1 µm), the number of particles in this class would be greatly reduced. However, the literature reports that up to 50% of airborne asbestos fibres have a length < 10 µm, and that approximately 30% of asbestos fibres have a length between 5 µm and 10 µm. Adoption of the additional criterion for class 2 would therefore have the effect of classifying these latter fibres as non-asbestiform particles and would exclude them from the asbestos fibre count (NIOSH, 2011).

Other procedures have been suggested for excluding cleavage fragments, including the study of available geological information and the analytical results for bulk samples, in order to establish the presence of asbestos or to specify the dimension criteria compatible with a population of asbestos fibres (for example, an aspect ratio > 20:1).

Lee (2005) formulated an addition to the MSHA definition of an asbestos fibre, namely a criterion about the presence of parallel sides. Thus, an amphibole fibre, whose width is generally from 0.2–0.3 µm, would be defined by: an aspect ratio > 20:1, parallel sides, regular ends, and an internal diffraction contour.

Chatfield (2008) also formulated discrimination rules for identifying an asbestos fibre:

- fibres $> 5 \mu\text{m}$ and $\leq 10 \mu\text{m}$ with aspect ratio $> 35:1$;
- fibres $> 10 \mu\text{m}$ and $\leq 20 \mu\text{m}$ with aspect ratio $> 30:1$;
- fibres $> 20 \mu\text{m}$ with aspect ratio $> 20:1$.

A research group has proposed a differential fibre counting methodology by PCM for air samples. NIOSH method 7400 has been improved by the use of a modified Walton & Beckett reticule allowing the measurement of particles $> 5 \mu\text{m}$ whose aspect ratio is greater than 3:1 and particles longer than $10 \mu\text{m}$ and of diameter less than or equal to $0.5 \mu\text{m}$. If 50% of the fibre population have a length equal to or greater than $10 \mu\text{m}$ or a diameter equal to or smaller than $0.5 \mu\text{m}$, the exposure is considered as being asbestiform. This type of sample must be reanalyzed by EM to evaluate its morphology, chemistry and crystalline structure. The percentage of equivalent optical fibres that corresponds to asbestos is therefore calculated and compared to reference values. A decision diagram for characterizing the asbestiform structure is presented in the report (Bailey *et al.*, 2004).

NIOSH (2011) mentions that it is very important that an analytical method capable of clearly distinguishing between asbestiform and non-asbestiform EMPs be developed, validated and used. However, it is still not clear whether these new procedures can suitably ensure the protection of exposed workers.

5.2.3 Occupational exposure to talc dust

Talc dust exposures occur during mining operations, milling, selection, bagging, loading and during the use of talc, as in the rubber industry and when talcs are added to ceramic and enamel clays. Since industrial talc is a mixture of different minerals, occupational exposure is associated with a mixture of mineral dusts including quartz and asbestos (tremolite/anthophyllite), present as contaminants in some deposits of this mineral. Talc deposits differ in their mineral composition, as shown in Table 2. Occupational exposure to talc dust has mainly been measured in mines and mills and in a few rubber plants, as summarized in Table 3. The information collected is mainly qualitative because the data are fragmentary and the description of the techniques is incomplete in the great majority of cases; documented airborne talc concentrations in the air must not be used as an evaluation of the exposure, nor to assess the risk.

To put the values in Table 3 in perspective, note that the very great majority of the locations greatly exceed the ACGIH permissible exposure values of 3 mg/m^3 for respirable dust, 0.025 for quartz, and 0.1 fibre/cubic centimetre of air (f/cc) for asbestos.

Table 3: Occupational exposure levels for talc

Identification and location	Talc concentration (mppcf ¹ , mg/m ³ or f/cm ³)	Analytical methods	Reference
Talcs from Austria and France	<p><u>Office employees</u>: No exposure (0.2 mg/m³) <u>Maintenance employees</u>, mechanics, etc.: < 5 mg/m³ (0.05–4.61 mg/m³) <u>Production workers</u>: >30 mg/m³, up to 159 mg/m³ <u>Other workers</u>: 5–30 mg/m³</p> <p>1988–2003: 1.46 mg/m³</p> <p>French site: <u>Electricians</u>: 2000–2004: 3.7 mg/m³ > 1990: 5.1 mg/m³ <u>Operators in the mill</u>: 1985–1989: 2.2 mg/m³ 1968–1982: estimated at 8 mg/m³ < 1968: estimated at 20 mg/m³ <u>Mill</u>: general exposure: 1986: 1.95 mg/m³ 2003: 0.80 mg/m³ <u>Cleaners</u>: 1985–1989: 11.3 mg/m³ <u>Office workers</u>: 0.16 mg/m³ 2000–2004: <u>Granulation area</u>, highest value: 9.7 mg/m³ <u>Automatic process</u>: 0.1 mg/m³, lowest value. <u>At extraction</u>: 1990: 0.67 mg/m³ 2003: 0.37 mg/m³ Highest exposures, in the <u>laboratory</u> where the samples are milled: 1990–1994: 18.8 mg/m³ 2000–2004: 5.6 mg/m³ Austrian site: <u>Mill</u>: 1988–1995: 0.75 mg/m³ 1996: 0.30 mg/m³ <u>At extraction</u>: 1992–1994: 0.65 mg/m³ 1994–2000: 0.32 mg/m³</p>	<p>Gravimetric analysis Personal sampling, respirable fraction</p> <p>Talc dusts, respirable fraction – gravimetric analysis; Personal sampling; CIP10</p> <p>Wearing of masks</p>	<p>Wild (2002)</p> <p>Wild (2008)</p>
Talc from Italy (Piedmont)	<p>> 1965: 0.8–3 mppcf (<u>mine</u>) 2–8 mppcf (<u>mill</u>) Fibres >5 µm: 0.01 f/cm³ (<u>mine and mill</u>)</p>	<p>Crystalline silica: 6% (mine); < 1% (mill)</p>	EPA (1992)

Identification and location	Talc concentration (mppcf ¹ , mg/m ³ or f/cm ³)	Analytical methods	Reference
Italy Val Chisone, Turin	<u>Miners</u> : 0.5–2.5 mg/m ³ (average 1.1 mg/m ³) 0.3–2.0 mg/m ³ (average 1.0 mg/m ³)	Respirable fraction Talc only (analytical methods not described)	Coggiola (2003) IARC (2010)
Italy (rubber plant)	1972: Total dusts: 5.4–199 mg/m ³ Fibres: 4.7–19.2 fibres > 5 µm/cm ³	2–3% silica fibres	EPA (1992)
Talc from Norway	1980–1982: 0.94–97.35 mg/m ³ (<u>mine</u>) 1.4–54.1 mg/m ³ (<u>mill</u>) Fibres: 0.2–0.9 f/ml Fibres of tremolite, anthophyllite and talc (definition of a fibre) Silica: < 1%	Total dusts (personal) PCM EM XRD	Wergeland (1990)
Talc from St. Lawrence County (Gouverneur)	>1945: 5–19 mppcf (<u>mine</u>) 7–36 mppcf (<u>mill</u>) 1972: 2–3 f > 5 µm/cm ³ (<u>mine</u>) 25–62 f > 5 µm/cm ³ (<u>mill</u>)	Sampling on membrane Fibre counting	Kleinfeld (1974) cited by EPA (1992)
NY State (north) Same deposit?	0.23–1.29 mg/m ³ (<u>mine</u>) 0.25–2.95 mg/m ³ (<u>mill</u>) Fibres > 5 µm: 4.5 f/cm ³ (<u>mine</u>) 5.0 f/cm ³ (<u>mill</u>); peak at 29.1 f/cm ³	EM: composition of fibres > 5 µm:	Dement (1980) cited in EPA (1992)
Industrial talc (tremolitic) Upstate New York	Concentration of estimated respirable talc: 0.1–1.7 mg/m ³	65% anthophyllite and 7% tremolite	Honda (2002)
Talc from Vermont (3 mines and mills)	Average concentration: 0.5–5.1 mg/m ³ (mine) 0.5–2.9 mg/m ³ (mill) Often > 20 mppcf (non-fibrous talc) Up to 60 f/cm ³	Respirable dusts Optical fibre count	EPA (1992) IARC (1987, 2010) Selevan (1979) Boundy (1979) Wegman (1982) Cited in EPA (1992)
Rubber plants	15–50 mppcf < 2 fibres > 5 µm/cm ³		Fine (1976) cited in EPA (1992), IARC (2010)
Talc from Georgia	<1970: average exposure: 32–855 mppcf (<u>mine</u>) 17–1672 mppcf (<u>mill</u>)		EPA (1992)
Tals: Montana Texas North Carolina	Average concentration (mg/m ³): 0.66 (mine); 1.1 (mill) 0.45 (mine); 1.56 (mill) 0.14 (mine); 0.26 (mill)	Respirable dusts	NIOSH (1979) cited in EPA (1992) IARC (2010)
Talc mines and mills in the United States	Median concentration: 1.20 mg/m ³ 90% of exposures > 2.78 mg/m ³	362 samples, respirable dusts, complete day	NIOSH (1979) cited in EPA (1992) and IARC (1987, 2010)

1: mppcf = Million particles per cubic foot

6. REGULATIONS AND RECOMMENDATIONS (ASBESTOS AND TALC)

In the United States, OSHA and the MSHA have the primary authority to regulate occupational exposures to asbestos. The EPA regulates asbestos exposures in the country and of government workers in states that are not covered by OSHA regulations. The Consumer Product Safety Commission (CPSC) regulates non-occupational asbestos exposures (for example, for users of consumer products, such as joint compounds). Government agencies and specific groups have addressed the questions involving carcinogenic agents, including asbestos: National Institute for Occupational Safety and Health (NIOSH), Agency for Toxic Substances and Disease Registry (ATSDR), American Conference of Governmental Industrial Hygienists (ACGIH), and the National Toxicology Program (NTP).

Organizations in other countries, the United Kingdom (Health and Safety Executive) and Germany (Deutsche Forschungsgemeinschaft), have also addressed the question of exposure to asbestos and to other carcinogens.

The International Agency for Research on Cancer (IARC) published a monograph on asbestos and the evidence for its carcinogenicity (IARC, 1987). IARC recently published monograph no. 93 on carbon black, titanium dioxide and talc (IARC, 2010).

6.1 Standards and recommendations

Several international and United States government (OSHA, MSHA, NIOSH, EPA) organizations have developed standards or recommendations on threshold limit values or acceptable values for asbestos, tremolite and talc. Moreover, in the regulations of several of these organizations, including OSHA and the MSHA, neither non-asbestiform amphiboles nor the cleavage fragments of non-asbestiform amphiboles are regulated as being asbestos.

A fibre longer than 5 μm and whose length:diameter ratio (aspect ratio) is greater than or equal to 3:1 corresponds to the definition most commonly used by standardization or regulation organizations. An upper limit of 3 μm for fibre diameter has also been retained to limit the counting of respirable fibres (WHO, 1987).

The occupational exposure limits (OELs) for talc and asbestos promulgated in different countries are reported in Table 4. In general, for talc, the values are from 0.25–2 mg/m^3 for respirable dust, and 2 mg/m^3 for inhalable or total dust. Québec differentiates non-fibrous talc at 3 mg/m^3 in respirable dust, and fibrous talc at 1 f/cm^3 . For asbestos, the predominant value is 0.1 f/cc . Québec has adopted a TWAEV (time-weighted average exposure value) of 1 f/cc , except for crocidolite and amosite, whose use is prohibited, and the TWAEV for installed materials is set at 0.2 f/cc . According to Gestis, Germany, France, Italy and the European Union do not have a specific value for talc. Limit values for dusts without specific effects were not documented by our literature search.

Table 4: Occupational exposure limits (OELs) – talc and asbestos¹

Country	Talc (mg/m ³)	Asbestos (f/cc)
Austria	2 – respirable aerosol	0.25 Short-term OEL: 1
Belgium	2 (without asbestos fibres)	0.1
Canada – Québec	Non-fibrous: 3 – respirable dust Fibrous talc ³ : 1 f/cm ³	(actinolite, anthophyllite, chrysotile, tremolite): TWAEV*:1 OEL short term: 5 (amosite, crocidolite): TWAEV*: 0.2 OEL short term: 1
Denmark	0.3 – respirable aerosol OEL short term: 0.6 – respirable aerosol	0.1 Short-term OEL: 0.2
European Union		0.1
France		0.1 ⁵
Germany (AGS) ²		0.1 ^{(a)(c)} 0.015 ^(b) 0.01 ^(d)
Hungary	2 – respirable aerosol	0.1
Italy		0.1
Japan	0,5 (respirable) ⁶ 2 (total) ⁶	2 ⁷
Netherlands	0.25 – respirable aerosol	0.01
Spain	2 – respirable aerosol	0.1
Sweden	2 – inhalable aerosol 1 – respirable aerosol	0.1
Switzerland	2 – respirable aerosol	0.01
United Kingdom	1 – respirable aerosol	0.1
United States (ACGIH)	2 ⁴	0.1
United States (NIOSH)	2 ⁴	0.1
United States (OSHA)	20 mppcf	

*: TWAEV: time-weighted average exposure value

¹ Taken from GESTIS International limit values 2006. Internationale Grenzwerte für chemische Substanzen: Valeurs limites internationales des substances chimiques. http://bgia-online.hvbg.de/LIMITVALUE/WebForm_gw.aspx² (a) Bindung Occupational Exposure Limit Value - BOELV (EU); (b) Reference value - individual measures are related to this LV; (c) workplace exposure concentration corresponding to the proposed tolerable cancer risk (see background document: Germany AGS); (d) workplace exposure concentration corresponding to the proposed preliminary acceptable cancer risk (see background document: Germany AGS)³ Notation of the ROHS (Regulation respecting occupational health and safety, in Québec): C1 (carcinogenic effect detected in humans)⁴ Containing no asbestos⁵ Over one hour⁶ IARC section 1.4 (IARC, 2010)⁷ Except amosite and crocidolite

6.2 History of the United States regulations

In 1986, OSHA revised the standard for occupational exposure to all forms of asbestos (asbestiform and non-asbestiform) to 0.2 f/mL (8 hours) (OSHA, 1986)⁵. Historically, exposure to ores considered as asbestos by OSHA is determined by the number of fibres with a length greater than 5 µm and whose length:diameter ratio (aspect ratio) is greater than or equal to 3:1, by using phase contrast microscopy (PCM). The use of this aspect ratio is common (supported by ACGIH and NIOSH), but it is not a universally accepted mineralogic criterion. Mineralogists consider mineral fibres as crystalline units that achieve their shape by growth, contrary to cleavage fragments that achieve their shape by fracturing. Campbell *et al.* (1979) proposed new criteria for defining asbestiform ores, by including only particles with a length greater than 5 µm, a diameter smaller than 3 µm, an aspect ratio greater than 20:1, as well as at least two of the following characteristics: parallel fibres occurring in bundles, fibres with splayed ends; fibres in the shape of fine needles; matted masses of individual fibres, and curved fibres.

In response to concerns about the mineralogic distinction between fibres and cleavage fragments, which could have biological implications, a scientific meeting on environmental and occupational health, organized by the ATS (American Thoracic Society), appointed a committee in 1988 to evaluate and critique the scientific knowledge on the health risks of tremolite exposures. From the mineralogic standpoint, the fundamental question was to know whether two fibrous particles of identical size and shape will have different biological properties, knowing that the first category of fibre acquired its shape by fracturing (cleavage fragments), contrary to the second category of fibre, which acquired its shape by geological growth (asbestiform fibres).

Subsequently, much confusion about the results of the toxicological studies prompted OSHA to once again revise its standards in 1992, and to withdraw its regulations on protection and prevention measures for exposure involving non-asbestiform asbestos due to a lack of evidence of health effects. In its evaluation, OSHA noted insufficient evidence that non-asbestiform ATAs (anthophyllite, tremolite, actinolite) represent a risk similar to their asbestiform homologues, mainly by using the extrapolation of data on asbestos. Evidence of a reliable confirmation was lacking : experimental animal studies showed the absence of or the minor effect produced by non-asbestiform ATAs, epidemiological studies on non-asbestiform ATAs are rather inconclusive, and the hypotheses of carcinogenicity seemed to offer only imprecise explanations. OSHA's evaluation did not contain substantial evidence for retaining the decision that non-asbestiform ATAs present a health risk similar to that of asbestos.

Since then, a few studies have revised the state of knowledge on tremolite, including NIOSH (2011), the EPA (2002) and the ATSDR (Agency for Toxic Substances and Disease Registry, 2001). Note that the last study is really a narrative review of the data, without a precise methodology or pre-established rules, and hence the difficulty evaluating the weight of the evidence. These organizations recommend prudence, considering the lack of evidence on health risks.

⁵ http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=PREAMBLES&p_id=790

7. EPIDEMIOLOGICAL STUDIES

7.1 Reviews

Since 1990, three major reviews have presented the results of epidemiological studies on the health effects of tremolitic talc, each with a slightly different purpose.⁶ They are:

- The American Thoracic Society (ATS), in 1990, whose aim was to evaluate the health risk of tremolite present in different ores including talc;
- The International Agency for Research on Cancer (IARC) which brought together a group of experts in 2006 to review the evaluation of the carcinogenicity of talc not containing asbestos or asbestiform fibres. A summary of the results was published by Baan (2007)⁷ and the final version came out in 2010, in IARC monograph No. 93 (IARC, 2010);
- Wild, in 2006, to update the epidemiological evidence on the carcinogenicity of talc not containing asbestiform fibres.

7.2 Scientific articles

A few scientific articles were not cited by the authors of the three major reviews either because they were published at a later date, or because they did not meet the selection criteria of the review in question, or for an undetermined reason. They are:

- Gibbs *et al.* (1992), talc pneumoconiosis;
- Gamble (1993), lung cancer in the New York cohort;
- Hull *et al.* (2002), mesothelioma in the New York cohort;
- Roggli *et al.* (2002), mineralogic analyses of the pulmonary retention of fibres of 312 mesothelioma cases;
- Honda *et al.* (2002), follow-up of the mortality survey on the New York cohort;
- Ramanakumar *et al.* (2008), case-control study on lung cancer;
- Wild *et al.* (2008), the effects of talc on respiratory health.

⁶ The comparative epidemiological review of Gamble and Gibbs is discussed in section B3.4.

⁷ IARC brought together a group of experts in 2009 that reviewed the carcinogenicity of talc, among other things. The results of this meeting will be published in monograph no. 100 and will contain the following note, under the term “asbestos”: mineral substances (e.g. talc or vermiculite) that contain asbestos should also be regarded as carcinogenic to humans.

(<http://monographs.iarc.fr/ENG/Classification/ClassificationsGroupOrder.pdf>, consulted 25/07/2010).

7.3 Other publications

Other organizations or authors have presented publications that, due to their format or methodology, do not lend themselves to analysis of the level of proof. The aim of each of these reviews gives a good indication of the variability in the approaches:

- OSHA (Occupational Safety and Health Administration) (1992), the evaluation of the effects on workers' health of non-asbestiform tremolite, anthophyllite and actinolite;
- G.D. Guthrie Jr. (1992), the dissemination of knowledge on the known biological effects of minerals inhaled by workers, to scientists in the mineral sector;
- E.B. Ilgren (2004), the demonstration that the toxicity of respirable cleavage fragments would be much lower than that for amphibole fibres, and that for all practical purposes, cleavage fragments would be biologically harmless;
- Gamble and Gibbs (2008), the comparison of the risks of lung cancer and mesothelioma for workers exposed to respirable cleavage fragments of amphiboles to workers exposed to analogous amphiboles that form asbestos fibres; and where one of the secondary objectives is to compare workers exposed to ore dusts containing amphibole cleavage fragments to workers exposed to similar ore dusts that do not contain asbestos or amphibole cleavage fragments;
- B. Price (2010), the aim of this review article (Industrial-grade talc exposure and the risk of mesothelioma) is not stated by the author. It is probably to prove that talc dust does not cause mesothelioma.

7.4 Articles not retained for the epidemiology section

The article by Srebro *et al.* (1994) entitled "Asbestos-Related Disease Associated With Exposure to Asbestiform Tremolite" was not retained because only one case, of the seven cases of mesothelioma examined by mineralogic analysis, appears to have been exposed to chrysotile and talc.

The article by Dodson *et al.* (1995) entitled "Quantitative Comparison of Asbestos and Talc Bodies in an Individual with Mixed Exposure" was rejected because it was a case history.

The article by Scancarello *et al.* (1996), "Respiratory Disease as a Result of Talc Inhalation," was not considered because it describes the history of three cases of workers exposed to talc dust in foundries. However, it illustrates the usefulness of characterizing the pulmonary burden to support the diagnosis and to propose causal links.

7.5 Summary of the results of epidemiological studies

Table 5 summarizes the results of the analysis of the scientific reviews and articles on talc dust inhalation exposure. Appendix B contains the details of the procedure for analyzing the scientific reviews and articles as well as a summary of other various publications.

Most organizations and epidemiologists that have been interested in the question of talc's carcinogenicity, such as IARC (2010) and Wild (2006), have differentiated exposure to talc without amphiboles from exposure to talc with amphiboles or other elongate mineral particles (EMPs), comparable to amphibole fibres, contrary to the ATS (1990). All these reviews arrive at an assessment of a lack of confirmation of pulmonary carcinogenicity of talc not containing asbestos or other asbestiform fibres. In addition, the ATS and Wild highlight the paucity of data on exposure.

The scientific articles that have been published without being cited in the reviews by the ATS, Baan, and Wild support the confirmation of absence of carcinogenicity of talc without asbestos or asbestiform fibres but fuel discussions on the presence or absence of cases of mesothelioma. However, two of these articles (Gibbs, 1992; Honda, 2002) as well as the publication by Gamble and Gibbs (2008) support the causality of talc in cases of pneumoconiosis.

The "other" publications, by using the same references, arrive at conclusions similar to those of Gamble and Gibbs (2008), to the effect that "pure" talc does not cause an increase in lung cancer or mesothelioma. However, NIOSH in its Current Intelligence Bulletin (NIOSH, 2011) concludes, based on American studies, that this observation about lung cancer is inconclusive, in contrast to negative evidence.

Table 5: Summary of the epidemiological studies related to talc exposure

Organization	Significant risk				Level of proof				Remarks
	A	P	M*	C	Ab	L	I	H	
Reviews									
ATS (1990)				no			x		All of the studies do not support the carcinogenicity of tremolite, asbestiform or not, in talc, but there are very few data on the tremolite content of talc.
Baan (2007) and IARC (2010)			0	no			x ⁸		Insufficient evidence for the carcinogenicity of inhaled talc that does not contain asbestos or asbestiform fibres (Group 3).
Wild (2006)				no			x		No mortality studies that indicate an increase in cancer risk. Few studies with appropriate information on exposure.
Mills									
Mines and user industries				Possible		x			Talc + other carcinogens.
Scientific articles									
Gibbs (1992)		yes				x			Shared causality between a variety of minerals. Supports the existence of talcosis in talc workers with almost no tremolite.
Gamble (1993)				no		x			Increase in risk with the number of years on the job; negative slope after adjustment for smoking. No dose-effect relationship. More congruent results with an etiology to tobacco than to talc.
Hull (2002)			5			x			Report on cases (5) without risk assessment except a tendency of an increase in the number of deaths by mesothelioma in the county (counties) between 1950 and 1997. No mention of occupational history.
Roggli (2002)			Yes**			x			Seems to indicate that tremolite originating from chrysotile and talc could be the causal agent and that tremolite is not eliminated during milling.
Honda (2002)				no		x			Concludes that there is a relationship with talc exposure for NMRD but not for excess cancer even though it was significant.
		yes					x		
Ramanakumar (2008)				no			x		Small number of workers exposed to high concentrations. More talc users than producers.
Wild (2008)	no						x		Small radiological opacities and respiratory functions significantly related to cumulative exposure at inclusion, but not to exposure during the study period.

A: NMRD P: pneumoconiosis, M: mesothelioma, C: lung cancer, Ab: absent, L: low, I: intermediate, H: high, *: indicates the number of observed cases of mesothelioma;

** : a mineralogic study of 312 cases of mesothelioma, 193 of which showed presence of talc

⁸ The group of experts classified talc in class 2B: possible human carcinogen by perineal route.

8. DISCUSSION AND CONCLUSION

8.1 Definitions and metrology (characterization and regulations)

Experts, analysts, researchers and government scientists have not reached a consensus on the definition of, or difference between, asbestiform and non-asbestiform amphiboles or cleavage fragments. While the distinction between cleavage fragments and asbestiform fibres is theoretically clear, it is rather obscure analytically. It is the analyst who chooses the most appropriate method based on the requirements and objectives of the analysis. Note that it is OSHA in its method ID-160 that specifies that “when in doubt, count” (OSHA, 1997).

Depending on the analytical method chosen, there are differences in the definition of a fibrous material, the definition of an asbestos fibre, and the counting rules. Despite the fact that several publications on differential analytical methods discuss criteria for differentiating amphibole asbestos (asbestiform) fibres from cleavage fragments (non-asbestiform amphiboles) (see section 5.2.2.3), most of these discussions are not incorporated into official analytical methods. From the analytical standpoint, the methods do not clearly describe how to arrive at decisions about what must be counted and not counted, and what constitutes a cleavage fragment.

There have been developments in the differential counting methodologies by PCM for air samples. By applying certain differential counting criteria, exposure can be considered as positive to asbestiform particles. However, the results must be confirmed by means of electron microscopy so as to properly evaluate the exposure in terms of morphology, chemistry and crystalline structure (Bailey *et al.*, 2004). The use of such complementary methods would confirm the presence of asbestos fibres and, more specifically with tremolitic talcs, determine the concentration of fibres, tremolite asbestiform fibres, cleavage fragments and talc fibres, if there were a consensus on the criteria to be used.

Most of the studies describing health effects related to talc exposure contain little information about the characterization of the talc involved. Even if the analytical methods characterized beyond all doubt the presence of amphiboles and quantified the asbestiform part and non-asbestiform part, it is still rather unlikely that toxicology studies can be carried out on completely pure products because talcs are generally a mixture of different minerals in variable concentrations.

Research to improve the sampling and analytical methods is necessary in order to: 1) reduce the inter-analyst and inter-laboratory variability; 2) develop a practical method for counting, measuring and identifying biologically active EMPs; 3) develop and validate selective sampling methods for collecting and quantifying fibres and other EMPs of thoracic particle size. These developments should have the following outcomes: identification of the physicochemical parameters (chemical composition, dimensions—length, diameter, aspect ratio—durability) as predictive of biopersistence, as well as the surface characteristics or oxidative stress activities in the determination of toxicity.

The expected research results could help define the analytical and sampling methods that will more suitably measure the relevant toxicity characteristics. The results should also contribute to the development of recommendations for worker protection (NIOSH, 2011).

8.2 Epidemiological studies

Table 5 summarizes the results of the reviews and scientific articles on inhalation exposure to talc dust. It indicates that the great majority of the studies since 1990 have addressed the issue of the carcinogenicity of “pure” talc and talc containing asbestos. It is clear that exposure to talc dust is associated with respiratory diseases such as NMRD, particularly pneumoconioses, and with lung cancer, in the presence of other carcinogenic agents. The possibility of mesothelioma remains a controversial subject.

8.2.1 NMRD

Since 1990, two articles contain the data on the already established consensus that talc ore dust can cause NMRD such as silicosis, talcosis and mixed pneumoconioses, but that the share of causality between talc, quartz and the other silicosis causative agents is not always identifiable. It was Honda (2002) for the New York cohort and Gamble and Gibbs (2008) who reported significant risks for the New York, Vermont and Italian cohorts, but non-significant risks for France,⁹ Austria and Norway. According to Gamble and Gibbs, the small number of NMRD cases in Norway is surprising, given the relatively high exposures.

8.2.2 Lung cancer

Millers do not present a significant increase in lung cancer risk but miners could show significant tendencies or increases in risk in the presence of other carcinogens such as radon, quartz or asbestos. In the user industries, the situation becomes more confused due to the presence of various other carcinogenic agents and the lack of data on exposure. Most of the organizations and epidemiologists that were interested in the question of the carcinogenicity of talc, such as IARC (Tables 5 and B2) and Wild (Tables 5 and B1.3), differentiated exposure to talc without amphiboles from exposure to talc with amphiboles or other components similar to amphiboles. All the studies have significant limitations such as the small number of cohorts or cases. There is no overall proof from the human epidemiological studies for claiming a causal relationship between talc without asbestiform fibres and lung cancer (Wild, 2006). In the same way, Gamble and Gibbs (2008) conclude that: “...‘pure’ talc does not cause an increase in lung cancer or mesothelioma.” Finally, based on American studies, NIOSH concludes in its Roadmap (NIOSH, 2011) that this observation about lung cancer is inconclusive, in contrast to negative evidence. The use of the dust or respirable dust concentration as exposure metric could be a poor predictor

⁹: Note that in France, the risk is not significant for NMRD but significant for pneumoconioses (SMR 3/0.5 = 5.56 (1.12–16.2)).

of the concentration of fibres or elongate mineral particles. The result is a possibility of incorrect classifications of cases, which complicates the establishment of a dose-response relationship.

8.2.3 Mesothelioma

Mesothelioma always presents the same difficulties in diagnosis and recognition of causality. As in the other asbestos exposure files, the number of cases varies significantly depending on whether they are identified by the authors from cancer registries or occupational compensation registries. In most of the cases of mesothelioma that were mentioned for talc workers, the diagnosis was questioned due to confusion about the classification codes, the presence of confounding agents, exposure in previous jobs, and the too short latency period. The low mesothelioma incidence rate, the existence of a certain percentage ($\approx 20\%$) of cases that are not explainable by asbestos exposure, and the small number of workers in most of the cohorts justify questioning the sufficient power of the studies to be able to make a statement about mesothelioma caused by talc ore dust. With the current state of knowledge, there is no evidence for linking mesothelioma and exposure to talc not containing asbestiform fibres.

8.2.4 Limitations of the interpretations of the epidemiological studies

In 1990, the ATS had to disregard the distinction between fibres and cleavage fragments, due to a lack of consensus between the experts about their identification and characterization (ATS, 1990). Wild, in his review on the carcinogenicity of talc not containing asbestos, deplors in his conclusion the rarity of studies with appropriate information on exposure (Wild, 2006). In 2008, Gamble and Gibbs end their article on the carcinogenicity of cleavage fragments by admitting that the results from the talc mines in New York and Vermont are inexplicable with the current state of our knowledge about the toxicity of these particles and the workers' exposure. With this observation, the NIOSH planning document (NIOSH, 2011) for the coming years recommends the following goals:

- Develop a broader and clearer understanding of the important determinants of toxicity for EMPs;
- Develop information on occupational exposures to various EMPs and health risks associated with such exposures;
- Develop improved sampling and analytical methods for asbestos fibres and other EMPs.

The epidemiological studies verified the dose-response relationship based on the time in employment, the average concentrations of respirable dusts, a few fibre concentration results by phase contrast microscopy or recently by electron microscopy, or evaluations by groups of experts. No study had concentration results for well characterized and well sampled cleavage fragments in the workers 'breathing zone'. In addition, based on our knowledge about asbestos and silica, it is very likely that the two metrics of mass and number of particles per volume of air are important for studying cleavage fragments.

Unfortunately, with the current state of knowledge from epidemiological studies, it is difficult to definitively answer, with supporting proof, the question about the health risks of these particles (cleavage fragments or elongate mineral particles).

As for their fibrogenicity, we have not found any epidemiological information since 1990 on the fibrogenic power of cleavage fragments. Due to the simultaneous presence of quartz, a powerful fibrogenic agent that is found in almost all mining locations for talc, asbestos fibres and other mineral particles, which can also have a certain activity, it is extremely difficult, if not impossible, to identify the share of causality of the different fibrogenic agents.

Regarding carcinogenicity, the comparison of cleavage fragments with amphibole fibres of the same composition seems to indicate that their carcinogenic power is less than that of asbestos. Some publications even go so far as stating that these particles are simply not carcinogenic. However, these comparative epidemiological procedures are difficult to evaluate due to the accumulation of hypotheses for comparing data but that can be misleading if they are not confirmed.

Also, tremolitic talc is only part of the problem of establishing the toxicity of elongate mineral fibres or cleavage fragments. Vermiculite has posed much more serious and obvious health problems than talc and wollastonite. Talc itself may be contaminated by other amphiboles than tremolite, mainly anthophyllite and actinolite. For certain mineral fibres such as attapulgite (palygorskite) (IARC classification: 2B for fibres $> 5 \mu\text{m}$), the scientific knowledge about health risks is extremely limited. As well, the question of the health risk from elongate mineral particles raises concerns about the different mining operations such as for grunerite, which can be found in some gold mines, and for taconite in iron extraction.

With the uncertainties about exposures and health effects, research is necessary in toxicology and epidemiology as well as on exposure, sampling measurements and analytical methods.

9. RECOMMENDATIONS

Since a conclusion cannot be reached about the biological effects from the distinction between cleavage fragments and asbestos fibres, the precautionary principle prompts the use of the same prevention measures with non-asbestiform fibres (cleavage fragments) as with asbestiform fibres of the same size.

When revisions are made to talc's carcinogenicity classification, this mineral should be considered as being a human carcinogen when it contains asbestos.

To substantiate the contribution of elongate mineral particles (EMPs) to pneumoconioses and cancer of the respiratory system, it is recommended that an EMP characterization and dosage strategy be developed that will complete the environmental portrait of the exposure of miners and millers as well as for potential users.

Since vermiculite, an ore widely used as insulation and in gardening products, may be contaminated with tremolite asbestos, other amphiboles, or EMPs, the same literature search procedure that was used for talc should be carried out.

Since it is rather unlikely that toxicology studies can be carried out on completely pure products because talcs are generally a mixture of different minerals in variable concentration, future research could help in defining the sampling and analytical methods that will more appropriately measure the relevant toxicity characteristics in order to establish a dose-response relationship in epidemiological studies. In addition, mineralogic studies of lung tissue (biometrology) could identify abnormal burdens and characterize the fibres and EMPs. The results of this research should also contribute to the development of recommendations for worker protection.

10. BIBLIOGRAPHY

American Conference of Governmental Industrial Hygienists (ACGIH). Documentation of the Threshold Limit Values and Biological Exposure Indices. Talc. (2010).

AFSSET. Les fibres courtes et les fibres fines d'amiant. Prise en compte du critère dimensionnel pour la caractérisation des risques sanitaires liés à l'inhalation d'amiant. (2009). http://www.afsset.fr/upload/bibliotheque/880943923695047004708603758030/fibres_courtes_a_miante_avis_rapport_Afsset_2009.pdf

American Society for Testing and Materials, ASTM Work Item WK3160 New Standard Test Method for Sampling and Counting Airborne Fibers, Including Asbestos Fibers, in Mines and Quarries, by Phase Contrast Microscopy, ASTM International, PA (2006).

American Society for Testing and Materials, ASTM D7200-06. Standard Practice for Sampling and Counting Airborne Fibers, Including Asbestos Fibers, in Mines and Quarries, by Phase Contrast Microscopy and Transmission Electron Microscopy (2006).

American Society for Testing and Materials, ASTM 6281-04, Standard Test Method for Airborne Asbestos Concentration In Ambient and Indoor Atmospheres as Determined by Transmission Electron Microscopy Direct Transfer (2004).

American Society for Testing and Materials, ASTM D5755-02, Standard Test Method for Microvacuum Sampling and Indirect Analysis of Dust by Transmission Electron Microscopy for Asbestos Structure Number Surface Loading (2002a).

American Society for Testing and Materials, ASTM D5756-02, Standard Test Method for Microvacuum Sampling and Indirect Analysis of Dust by Transmission Electron Microscopy for Asbestos Mass Surface Loading (2002b).

American Society for Testing and Materials, ASTM 6480-99, Standard Test Method for Wipe Sampling of surfaces, Indirect Preparation, and Analysis for Asbestos Structure Number Concentration by Transmission Electron Microscopy (1999).

American Thoracic Society, Health Effect of Tremolite. American Review of Respiratory Disease. 142(6): 1453-1458 (1990).

ATSDR (Agency for Toxic Substances and Disease Registry). Tremolite Asbestos Health Consultation. Chemical-Specific Health Consultation: Tremolite Asbestos and Other Related Types of Asbestos. (2001). http://www.atsdr.cdc.gov/asbestos/more_about_asbestos/health_consultation

Baan R.A. Carcinogenic hazards from inhaled carbon black, titanium dioxide, and talc not containing asbestos or asbestiform fibers: recent evaluations by an IARC Monographs Working Group. *Inhal Toxicol.* 19 Suppl 1:213-28 (2007).

Baan R.A. Carcinogenicity of Carbon Black, Titanium Dioxide and Non-Asbestiform Talc. *Summaries and Evaluations. The Lancet Oncology.* 7(6): 295-296 (2006)

Bailey K.F., Wylie A.G. , Kelse J. and Lee R.J. The Asbestiform and Prismatic Mineral Growth Habit and Their Relationship to Cancer Studies. A Pictorial Presentation, March 2004.

<http://www.cdc.gov/niosh/docket/archive/pdfs/NIOSH-099A/0099A-030104-Pictorialpresentation.pdf>

Campbell W.J., Steel E.B., Virta R.L. and Eisner M.H. Characterization of cleavage fragments and asbestiform amphibole particulates. In: R. Lemen, J.M. . (Eds.), *Dusts and Disease*. Pathotox Publishers, Park Forest South, Illinois, pp. 276-285 (1979).

Chatfield E. A procedure for quantitative description of fibrosity in amphibole minerals. *Communication. Johnson Conference.* (2008).

Coggiola M., Bosio D., Pira E., Piolatto P.G., La Vecchia C., Negri E., Michelazzi M. and Bacaloni A. An Update of a Mortality Study of Talc Miners and Millers in Italy. *American Journal of Industrial Medicine.* 44:63-69 (2003).

Cullinan P. and McDonald J.C. Respiratory disease from occupational exposure to non-fibrous phyllosilicates. *NATO ASI Series, Vol. G21, Health Related Effects of Phyllosilicates*, Edited by J. Bignon. Springer-Verlag Berlin Heidelberg. (1990).

Dodson R.F., O'Sullivan M., Corn C.J. and Hamar S.P. Quantitative comparison of asbestos and talc bodies in an individual with mixed exposure. *Am J. Ind. Med.* 27(2): 207-215 (1995).

EPA (U.S. Environmental Protection Agency). Method for the Determination of Asbestos in Bulk Building Materials. EPA-600/R-93/116, July 1993. <http://www.rti.org/pubs/Test-Method-for-Determination.pdf>

EPA (U.S. Environmental Protection Agency). Health Assessment Document for Talc. EPA-600/8-91/217, March 1992.

EPA (U.S. Environmental Protection Agency). Code of Federal Regulations. 40 CFR – Part 763 – Asbestos (2003). <http://www.epa.gov/asbestos/pubs/2003pt763.pdf>

J.F. Gamble and G. W. Gibbs. An evaluation of the risks of lung cancer and mesothelioma from exposure to amphibole cleavage fragments. *Regulatory Toxicology and Pharmacology.* 52:S154–S186 (2008).

Gamble J.F. A nested case control study of lung cancer among New York talc workers. *Int. Arch. Occup. Environ. Health.* 64:449-456 (1993).

Gibbs A.E., Poole F.D., Griffiths D.M., Mirtha R., Craighead J.E. and Ruttner J.R. Talc pneumoconiosis: A pathologic and mineralogic study. *Hum. Pathol.* 23:1344-1354 (1992).

Guthrie G.D. Jr. Biological Effects of Inhaled Minerals. *The American Mineralogist.* 77 (3-4): 225-243 (1992).

Harper M., Lee E.G., Doorn S.S. and Hammond O. Differentiating Non-Asbestiform Amphibole and Amphibole Asbestos by Size Characteristics. *Journal of Occupational and Environmental Hygiene.* 5:761-770 (2008).

Health and Safety Executive (HSE). Methods for the Determination of Hazardous Substances (MDHS) 39/4, Asbestos fibres in air – Sampling and evaluation by phase contrast microscopy (PCM) under the Control of Asbestos at Work Regulations. London, HSE (1995).

Honda Y., Beall C., Delzell E., Oestenstad K., Brill I. and Matthews R. Mortality among Workers at a Talc Mining and Milling Facility. *Ann. Occup. Hyg.* 46(7): 575-585 (2002).

Hull M.J., Abraham J.L. and Case B.W. Mesothelioma among Workers in Asbestiform Fiber-bearing Talc Mines in New York State. *Ann. Occup. Hyg.*, 46: Supplement 1, 132–135 (2002).

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of the carcinogenic risk of chemicals to humans. Carbon Black, Titanium Dioxide, and Talc. Vol. 93, 477 p. (2010).

IARC (International Agency for Research on Cancer). Talc. Perineal use of talc-based body powder (Group 2B). Inhaled talc not containing asbestos or asbestiform fibres (Group 3). Summary of Data Reported. Vol. 93 (2006).

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of the carcinogenic risk of chemicals to humans. Silica and some silicates. Vol. 42. 289 p. (1987).

Ilgren E.B. The biology of cleavage fragments: A brief synthesis and analysis of current knowledge. *Indoor Built Environ.* 13:343-356 (2004).

International Organization for Standardization, ISO 14966, Ambient Air -- Determination of Numerical Concentration of Inorganic Fibrous Particles - Scanning Electron Microscopy Method (2002)

International Organization for Standardization, ISO 13794, Ambient Air – Determination of Asbestos Fibres – Indirect-Transfer Transmission Electron Microscopy Method (1999).

International Organization for Standardization, ISO 10312, Ambient Air – Determination of Asbestos Fibres – Direct-Transfer Transmission Electron Microscopy Procedure (1995).

International Organization for Standardization, ISO 8672, Air Quality - Determination of the number concentration of airborne inorganic fibres by phase contrast optical microscopy - Membrane filter method (1993).

Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST). Numération des fibres. Méthode 243-1. In Méthodes de laboratoires: Méthodes analytiques. Montréal. IRSST (1991).

Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST). Caractérisation des fibres dans les poussières déposées ou dans les matériaux en vrac. Méthode 244-2. In Méthodes de laboratoires: Méthodes analytiques. Montréal. IRSST (1999).

Jones A.D., Aitken R.J., Fabriès J.F., Kauffer E., Liden G., Maynard A., Riediger G. and Sahle W. Thoracic Size-Selective Sampling of Fibres: Performance of Four Types of Thoracic Sampler in Laboratory Tests. *Ann. Occup. Hyg.* 49(6) 481-492 (2005).

Kirk-Othmer. *Encyclopedia of Chemical Technology*, 3rd ed., Vol. I, Wiley-Interscience, New-York, 1978.

Langer A.M., Nolan R.P. J. Addison J. Distinguishing between amphibole asbestos fibers and elongate cleavage fragments of their non-asbestos analogues. In: *Mechanisms in Fibre Carcinogenesis*. Edited by R.C. Brown *et al.*, Plenum Press, New York. Pp 253-267 (1991).

Lee E.G., Nelson J., Hintz P.J., Joy G., Andrew M.E. and Harper M. Field performance of the CATHIA-T sampler and two cyclones against the standard cowled sampler for thoracic fiber concentrations. *Ann Occup Hyg.* 54:545-556 (2010).

Lee E.G., Harper M., Nelson J., Hintz P.J. and Andrew M.E. A comparison of the CATHIA-T sampler, the GK2.69 cyclone and the standard cowled sampler for thoracic fiber concentrations at a taconite ore-processing mill. *Ann Occup Hyg.* 52:55-62 (2008).

Lee R.J., Strohmeier B.R., Bunker K.L. and Van Orden D.R. Naturally occurring asbestos – A Recurring Public Policy Challenge. *Journal of Hazardous Materials.* 153:1-21 (2008).

Lee R.J. Letter. Comments Related to Proposed MSHA Asbestos Regulations. (2005). <http://www.msha.gov/regs/comments/05-14510/1219-ab24-comm-108.pdf>

Leophonte P. and Didier A. French talc pneumoconiosis. In *Health-Related Effects of Phyllosilicates*. NATO ASI Series. Edited by J. Bignon. Springer-Verlag Berlin Heidelberg. Vol. G21, pp 203-209 (1990).

Maynard A. Thoracic Size-Selection of Fibres: Dependence of Penetration on Fibre Length for Five Thoracic Samplers. *Ann. Occup. Hyg.* 46: 511–22 (2002).

MDHS. Asbestos in Bulk Materials - Sampling and Identification by Polarised Light Microscopy (PLM). Health & Safety Executive (1994). Traduction de la monographie par l'INRS. Cahier de notes documentaires – Hygiène et sécurité du travail. 166: 17-35 (1997). [http://www.inrs.fr/inrs-pub/inrs01.nsf/IntranetObject-accesParReference/HST_ND%202038/\\$File/ND2038.pdf](http://www.inrs.fr/inrs-pub/inrs01.nsf/IntranetObject-accesParReference/HST_ND%202038/$File/ND2038.pdf)

MDHS. Asbestos in Bulk Materials - Sampling and Identification by Polarised Light Microscopy (PLM). Health & Safety Executive. Method 77 (1994).

Meeker G.P., Bern A.M., Brownfield I.K., Lowers H.A., Sutley S.J., Hoefen T.M. and Vance J.S. The Composition and Morphology of Amphiboles from the Rainy Creek Complex, Near Libby, Montana. *American Mineralogist*. 88: 1955-1969 (2003).

Millette J.R. and Bandli B.R. Asbestos Identification Using Available Standard Methods. *Microscope*. 53:4: 179-185 (2005).

Mine Safety and Health Administration (MSHA). Asbestos Exposure Limit; Proposed Rule. *Federal Register*. 70:145, 30 CFR, Parts 56, 57 and 71 (2005).

<http://www.msha.gov/regs/fedreg/proposed/2005prop/05-14510.asp>

National Toxicology Program (NTP). Toxicology and carcinogenesis studies of talc in Fischer 344/N rats and B6C3F1 mice. (Inhalation studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH Publication No. 93-3152. NTP TR 421 (1993)

National Institute for Occupational Safety and Health (NIOSH). Asbestos and other fibers by PCM. Method 7400. NIOSH Manual of Analytical Methods (NMAM), 4th ed. (1994a).

National Institute for Occupational Safety and Health (NIOSH). Asbestos by TEM. Method 7402. NIOSH Manual of Analytical Methods (NMAM), 4th ed. (1994b)

National Institute for Occupational Safety and Health (NIOSH). Comments to DOL. Comments of the National Institute for Occupational Safety and Health on The Occupational Safety and Health Administration's notice of proposed rulemaking on occupational exposure to asbestos, tremolite, anthophyllite, and actinolite. 29 CFR Parts 1910 and 1926. Docket No. H-033d (1990). http://www.cdc.gov/niosh/review/public/099/pdfs/AsbestosTestimony_April%209_1990.pdf

NFX 43-050. Qualité de l'air – Détermination de la concentration en fibres d'amiante par microscopie électronique à transmission – Méthode indirecte. AFNOR (1996).

NIOSH. CURRENT INTELLIGENCE BULLETIN 62. Asbestos Fibers and Other Elongate Mineral Particles: State of the Science and Roadmap for Research. Department of Health and Human Services. Centers for Disease Control and Prevention. National Institute for Occupational Safety and Health. Publication No. 2011-159. March 2011. <http://www.cdc.gov/niosh/docs/2011-159/pdfs/2011-159.pdf>

Occupational Safety and Health Administration (OSHA). Occupational Exposure to Asbestos, Tremolite, Anthophyllite and Actinolite. *Federal Register*. 57:110, 29 CFR Parts 1910 and 1926, Docket NO H-033-d.24310 (1992).

Occupational Safety and Health Administration (OSHA). Polarized Light Microscopy of Asbestos. Analytical Method OSHA ID-191 (1992). <http://www.osha.gov/dts/sltc/methods/inorganic/id191/id191.html>

Occupational Safety and Health Administration (OSHA). Asbestos in air. Analytical Method OSHA ID-160 (1997). <http://www.osha.gov/dts/sltc/methods/inorganic/id160/id160.html>

Paoletti L., Caiazza S., Donelli G. and Pocchiari F. Evaluation by Electron Microscopy Techniques of Asbestos Contamination in Industrial, Cosmetic, and Pharmaceutical Talc. *Regulatory Toxicology and Pharmacology*. 4:222-235 (1984).

Pooley F.D. and N. Rowlands N. Chemical and physical properties of British talc powders. In: Walton, W.H.; McGovern, B., eds. *Inhaled particles IV: proceedings of an international symposium, part 2: September 1975; Edinburgh, UK: Pergamon Press*. 4(2): 639-646 (1977).

Price B. Industrial-grade talc exposure and the risk of mesothelioma. *Critical Reviews in Toxicology*, 40(6): 513-30 (2010).

Ramanakumar A.V., Parent M.E., Latreille B. and Siemiatycki J. Risk of lung cancer following exposure to carbon black, titanium oxide and talc: Results from two case-control studies in Montreal. *Int. J. Cancer*. 122: 183-189 (2008).

Risk & Policy Analysts Limited, Comparative Study on Cosmetics Legislation in the EU and Other Principal Markets with Special Attention to so-called Borderline Products. http://ec.europa.eu/enterprise/newsroom/cf/_getdocument.cfm?doc_id=4557

Roggli V.L., Vollmer R.T., Butnor K.J. and Sporn T.A. Tremolite and Mesothelioma. *Ann. Occup. Hyg.* 46: 447-453 (2002).

Scancarello G., Romeo R. and Sartorelli E. Respiratory Disease as a Result of Talc Inhalation. 38(6): 610-614 (1996).

Selevan S.G., Dement J.M., Wagoner J.K. and Froines J.R. Mortality patterns among miners and millers of non-asbestiform talc: preliminary report. *Journal of Environmental Pathology and Toxicology*. 2:273-284 (1979).

Siegrist H.G. and Wylie A.G. Characterizing and discriminating the shape of asbestos particles. *Environ Res*. 23:348-361 (1980).

Skinner, H.C.W., Ross M. and Frondel C. *Asbestos and other fibrous materials—Mineralogy, crystal chemistry, and health effects*: New York, Oxford University Press, 204 p. (1988).

Srebro S.H. and Roggli V.L. Asbestos-Related Disease Associated With Exposure to Asbestiform Tremolite. *Am J. Ind. Med.* 26(6): 809-819 (1994).

USGS (U.S. Geological Survey). *Tabulation of Asbestos-Related Terminology*. By Heather Lowers and Greg Meeker. Open-file Report 02-458 (2002).

Van Gosen B.S. The Geology of asbestos in the United States and its practical application. *Environ Eng Geosci* 13: 55-68 (2007).

Veblen D.R. and Wylie A.G. Mineralogy of amphiboles and 1:1 layer silicates. In: G.D. Guthrie and B.T. Mossman, eds. *MSA Reviews in Mineralogy*. Vol. 28: 61-137 (1993).

Virta R.L. Talc and pyrophyllite. In: US Geological survey Minerals Yearbook – 2008. Pp 75.1 – 75.8. (2009a). <http://minerals.usgs.gov/minerals/pubs/commodity/talc/myb1-2008-talc.pdf>

Virta R.L. Talc and pyrophyllite. In: US Geological survey Minerals Yearbook – 2008. Pp 75.1 – 75.8. (2009b). <http://minerals.usgs.gov/minerals/pubs/commodity/talc/mcs-2009-talc.pdf>

VDI (Verein Deutscher Ingenieure). Indoor air measurement - Ambient air measurement - Measurement of inorganic fibrous particles - Scanning electron microscopy method, VDI 3492 (2004).

Wergeland E., Andersen A. and Baerheim A. Morbidity and mortality in talc-exposed workers. Am. J. Ind. Med. 17: 505-513 (1990).

Wild P., Leodolter K., Réfrégier M., Schmidt H. and Bourgkard E. Effects of talc on respiratory health: results of a longitudinal survey of 378 French and Austrian talc workers. Occup. Environ. Med. 65: 261-267 (2008).

Wild P. Lung cancer risk and talc not containing asbestiform fibres: a review of the epidemiological evidence. Occup. Environ. Med. 63: 4-9 (2006).

Wild P., Leodolter K., Schmidt H., Zidek T. and Haidinger G. A cohort mortality and nested case-control study of French and Austrian talc workers. Occup. Environ. Med. 59: 98-105 (2002).

World Health Organization (WHO). Determination of airborne fibre number concentrations, A recommended method, by phase-contrast optical microscopy (membrane filter method). Geneva: WHO (1997).

Zazenski R., Ashton W.H., Briggs D., Chudkowski M., Kelse J.W., MacEachern L., McCarthy E.F., Nordhauser M.A, Roddy M.T., Teetsel N.M., Wells A.B. and Gettings S.D. Talc: Occurrence, Characterization, and Consumer Applications. Regulatory Toxicology and Pharmacology. 21:218-229 (1995).

XP X 43-269. Qualité de l'air – Air des lieux de travail – Détermination de la concentration en nombre de fibres par microscopie optique en contraste de phase – Méthode du filtre à membrane. AFNOR (2002).

APPENDIX A: SYNONYMS AND COMMERCIAL NAMES OF TALC

Commercial names for industrial, cosmetic and pharmaceutical talcs¹⁰ including:

Agalite	Mistron
Asbestine	Montana talc
Australian microcrystalline	MP 25-38
Beaver White 200	MP 40-27
Ceramitalc HDT	MP 45-26
Ceramitalc No. 1	MST
CP-10-40	MT 12-50
CP 38-33	Mussolinite
Crystalite CR 6002	NCI-CO6018
Desertalc 57	Nytaal 14
Emtal 500	Nytaal 200
Emtal 549	Nytaal 300
Emtal 596	Nytaal 400
Emtal 599	Pk-C
Ex-IT	Pk-N
Fibrene C 400	Plustalc
Finntalc	Polytaal 4641
French Chalk	Polytaal 4725
FW-XO	Snowgoose
HSDB 830	Steawhite
IT 3X	Supreme
IT Extra	Supreme dense
LMR 100	Talcan PK-P
Microneeca K1	Talcron CP 44-31
Micro White 5000A	Westmin
Microtalco IT Extra	

¹⁰ Adapted from IARC (2010), p. 278.

APPENDIX B: EPIDEMIOLOGICAL STUDIES

Appendix B1. Reviews

B1.1 ATS (1990)

Table B1 summarizes the evaluations of the ATS committee of experts on talc contamination by tremolite, carried out in 1990. A detailed description of the epidemiological data from most of the articles cited by the ATS can be consulted in Appendices C and D, as presented by Wild (2006) and IARC (2010). The ATS, in its official statement, set the goal of evaluating the health risk of tremolite. When it was impossible to establish a scientific consensus between cleavage fragments and asbestiform fibres on the one hand, and asbestiform and non-asbestiform fibres on the other, the ATS treated all of the data under the generic term of “fibres” of different dimensions by stressing the need for pursuing research on the characterization of these exposures.

New York Cohort

The first four studies mentioned by the ATS (Table B1) describe the situation in the talc mine in New York State (Gouverneur Talc mine and mill: New York 1, 2 and 3 as well as the NIOSH cohort). Only the first study reported a high level of pneumoconiosis (27% of deaths), one case of mesothelioma and an excess risk of lung cancer (13 cases, or 12% of deaths compared to 3.7% expected on the basis of the 1955 American rate) with a “low” level of proof, due to a lack of information on smoking, the absence of dose-response relationship, and the lack of exposure data for other fibrogenic agents. New York studies 2 and 3 were considered by the ATS as unsuitable for risk evaluation. The case-control study (NIOSH study) concluded that there was a lack of significant risk of lung cancer, given that the sole significant risk of lung cancer was in workers with less than one year of experience (SMR: 357.2 one-tailed $p < 0.01$; 8 observed cases out of 2.3 expected cases) while workers with more than one year of experience did not show a significant risk (5 observed cases, 2.81 expected cases, one-tailed $p > 0.15$) after adjustment for smoking. The authors did not observe any dose-response relationship. The level of proof of the lack of significance was evaluated as “intermediate” rather than “high,” based on the significant risk in workers with less than one year of experience and on the possibility of one mesothelioma.

This location was the subject of many epidemiological studies, some of which will be described in subsequent sections,¹¹ and of characterizations of the exposure which are mentioned in Table 3 in section 5.4.3.

Vermont Cohort

The Vermont cohort is described as a talc-without-asbestos mine. The sole identified study presents a significant increase in risk of lung cancer in miners (5/1.15, SMR = 4.35 (1.41–10.1)) which does not appear in millers (2/1.96, SMR = 1.02 (0.12–3.68)). The level of proof is “low” due to the lack of information on exposure to different agents, of a dose-response relationship, and of data on smoking. No follow-up could be found during the literature searches.

¹¹: The background of studies on talc from Gouverneur Talc was described by Gamble and Gibbs (2008)

Italian cohort

The ATS provides very few details about this mine that produces pure talc that may contain small amounts of tremolite. The cohort of 2000 workers has shown an excess of pneumoconioses possibly attributable to crystalline silica, but no evidence of an increased risk of lung cancer. No data are provided by the ATS but an update is reported in the reviews of Baan (IARC) and Wild.

User industries

The National Cancer Institute collected the data on a cohort of three ceramics industries, and divided them into three groups: without talc exposure, with exposure to fibrous talc (tremolitic), and with exposure to non-fibrous talc (containing no asbestos fibres). Only the group of workers with exposure to non-fibrous talc (without asbestos) had a significant risk of lung cancer (21/8.3, SMR = 2.54; $p < 0.001$). However, several methodological limitations reduce the study's reliability: all the workers may have had a high exposure to crystalline silica, a lack of information on smoking, the small number of workers exposed to fibrous talc, and the use of the national rather than the local mortality rate, resulting in a "low" level of proof.

Conclusion

According to the ATS in 1990, all of the studies do not support the carcinogenicity of tremolite, asbestiform or not, in talc. The level of proof of the different studies is "intermediate" for NMRD and "low" for lung cancer and mesothelioma.

Table B1: Analytical grid – Reviews – ATS 1990 - Workers

ATS. Health effects of tremolite. (Am Rev Respir Dis. 142(6): 1453-1458, 1990).										
Official statement of the American Thoracic Society (ATS) adopted by the board of directors in June 1990.										
Literature review and evaluation of risk of occupational contamination by tremolitic talc.										
With the impossibility of establishing a scientific consensus between cleavage fragments and asbestiform fibres on the one hand, and asbestiform and non-asbestiform fibres on the other, the ATS treats all of the data under the generic term of "fibres" of different dimensions.										
Summary		Significant risk				Level of proof				Remarks
		A	P	M*	C	Ab	L	I	H	
Mines and mills										
New York 1 (New York mine) Kleinfeld <i>et al.</i> , 1967 and 1974 ¹²			yes				x**			Numerous cases of pneumoconioses that may be caused by talc as much as by tremolite.
				1	yes		x			Proportional mortality study. One peritoneal mesothelioma.*** Without data on exposure, impossible to establish causality of tremolite. Contamination by asbestiform tremolite, excess risk of lung cancer but no data on smoking and no dose-response relationship, methodological problem inherent in proportional mortality study, comparison with the US cancer rate while New York > US, between 1950 and 1959.
New York 2 (New York mine) Brown <i>et al.</i> , 1979										1947–1959 Limitations in the analysis of the data which prevent any decision about risk. No exposure data and variability in the consideration of previous jobs and follow-up. NIOSH studies.
New York 3 (same mine as 2, 2 studies) Stille <i>et al.</i> , 1982 Lamm <i>et al.</i> , 1988										1948–1977 Limitations in the data analysis, which prevent any decision about risk. NIOSH studies.
New York NIOSH (same mine as 2) Gamble <i>et al.</i> , (unpublished)					no			x		1947–1983 Significant risk of cancer only in workers with less than one year of service. The results of the case-control study with correction for smoking and the lack of dose-response relationship do not support the causal relationship between the risk and tremolite exposure in talc mines.
Vermont NIOSH Selevan <i>et al.</i> , 1979.										Talc mine without asbestos.
Mill					no		x			Increased risk in miners but not in millers.
Mine					yes		x			(1947–1959) Lack of information on exposure to different agents. No dose-response relationship. No information on smoking and other confounding factors.

¹²: The name of the first author of the article as cited by the ATS and the year of publication are inserted to facilitate comparison with the other tables and the text

<i>Italian cohort</i> Rubino <i>et al.</i> , 1976		yes		no			x		Very pure talc (small amount of tremolite). 2000 workers. Excess pneumoconiosis possibly attributable to crystalline silica.
	User industries								
<i>NCI Cohort (National Cancer Institute)</i> Thomas <i>et al.</i> , 1987	Three ceramics industries. Workers with high exposure to crystalline silica								
				no					No talc exposure.
				no					Fibrous talc (tremolitic).
				yes		x			Non-fibrous talc (without asbestos). Significant risk of cancer with dose-response relationship (methodological limitations).
General conclusion				no			x		All of the studies do not support the carcinogenicity of tremolite, asbestiform or not, in talc.

A: NMRD, P: pneumoconiosis, M: mesothelioma, C: lung cancer, Ab: absent, L: low, I: intermediate, H: high;

*: indicates the number of observed cases of mesothelioma;

**: the ATS does not go into detail on the pneumoconiosis data, focusing mainly on carcinogenicity;

***: Gamble and Gibbs describe it as a pleural mesothelioma.

B1.2 Baan (2007) and IARC (2010)

The International Agency for Research on Cancer (IARC) brought together a group of experts on February 26, 2006, to review the evaluation of the carcinogenicity of talc. Baan published in *Lancet* a summary of the experts' discussions (Baan, 2006) that provides the essential elements but that does not allow the level of proof to be established (Table B2). This section was completed when IARC monograph 93 was available, in 2010. A detailed description of the epidemiological data from the different articles can be consulted in Appendix C, in Tables C1 to C4 (taken from Wild, 2006) and in Appendix D, in Tables D1 and D2 (taken from IARC, 2010).

Italian cohort

IARC describes the initial article on the Italian cohort (Rubino *et al.*, 1976) and the second analysis in 1979 (Rubino *et al.*, 1979). The ore is presented as very pure talc with less than 2% quartz and the occasional presence of tremolite in some samples. The dose was evaluated in mppcf, meaning as a dust concentration. The risks of pneumoconiosis (62 cases; SMR, 2.0; (95% CI, 1.5–2.6) and of pneumoconiosis worsened by tuberculosis (18 cases; SMR, 2.0; 95% CI, 1.2–3.1) are significant. These estimates increase with the exposure. The cancer risk is not significant. Smoking was not taken into account. In addition, the group of experts noted the lack of comparability between the workers and the control group. No mesothelioma was observed.

Vermont cohort

The Vermont cohort in the United States gave an increased risk of lung cancer that is statistically significant in miners (seven cases; SMR, 4.3; 95% CI, 1.4–10.1) that is not observed in millers (two cases; SMR, 1.0; 95% CI, 0.1–3.7). However, NMRD gave different results, from non-significant in miners (two cases; SMR, 1.6; 95% CI, 0.2–5.9) to significant in millers (seven cases; SMR, 4.1; 95% CI, 1.6–8.4).

Norwegian cohort

The study of the Norwegian cohort detected no excess significant risk for lung cancer, pneumoconioses and mesothelioma.

French cohort

For pneumoconioses, a significant SMR of 5.6 (95% CI, 1.1–16.2), whose statistical significance disappears with the use of pre-1968 national reference rates rather than post-1968 ones. No statistically significant increase in lung cancer (21 cases; SMR, 1.2; 95% CI, 0.8–1.9) was observed even though the groups under sixty years of age with a latency period of less than 20 years or a duration of employment of less than ten years indicated SMRs greater than 2 but that were not significant.

Austrian cohort

No increased lung cancer risk (7 cases; SMR, 1.1; 95% CI, 0.4–2.2) was noted for this cohort. Some unpublished information on smoking is available but its use in the risk evaluation is not indicated. The actual number in the cohort is not clearly determined. No mesothelioma was observed.

French and Austrian cohorts

The cases of lung cancers from the two cohorts, French and Austrian (Wild *et al.*, 2000 and 2002), were combined to allow a case-control analysis with cumulative exposure from various sources. The results of the unadjusted risk ratios (OR) are:

- 0.9 (1–100 mg/m³–years; six cases, 18 controls);
- 1.1 (101–400 mg/m³–years; seven cases, 15 controls);
- 0.6 (401–800 mg/m³–years; five cases, 21 controls);
- 0.7 (> 801 mg/m³–years; three cases, 10 controls).

By assuming a linear relationship, the OR was 1.0 (95% CI, 0.9–1.1) per 100 mg/m³–years. The adjustment for smoking, quartz exposure and underground work, of one or two of these variables, did not change the result.

Italian cohort

The Italian cohort showed a significant risk of NMRD (105 cases; SMR, 3.1; 95% CI, 2.5–3.7), 58 of which were silicoses. No mesothelioma and no increased risk of lung cancer (44 cases;

SMR, 0.9; 95% CI, 0.7–1.3) were observed. In this study, as reported by IARC, there is no information about smoking and about the dust concentrations.

Québec cohort

This community-based case-control study indicated no increased risk of lung cancer (risk ratio (OR): 0.9 (35 exposed cases; 90% CI, 0.6–1.4)) for users of “industrial” talc. The main disadvantages of this approach are the indirect estimation of exposure by experts and the preponderance of low exposures compared to higher exposures in the workplace. The advantages are good information on smoking and on other exposures to various substances.

User industry

IARC reported the results of a single epidemiological study on lung cancer, in a talc-using industry, namely the manufacture of ceramic plumbing equipment. However, limited knowledge can be gained from this study due to the preponderant presence of respirable quartz. The excess mortality by lung cancer in workers exposed to high concentrations of quartz was statistically significant (44 cases; SMR, 1.8; 95% CI, 1.3–2.4). This increase was accentuated in the subgroups exposed to non-fibrous talc in addition to quartz (21 cases; SMR, 2.5; 95% CI, 1.6–3.9) while it became non-significant in the subgroups with additional exposure to fibrous talc (5 cases; SMR, 1.7; 95% CI, 0.6–4.0) or without exposure to talc (18 cases; SMR, 1.4; 95% CI, 0.8–2.2).

Table B2: Analytical grid – Reviews – Baan (2007) and IARC (2010)

Carcinogenic Hazards from Inhaled Carbon Black, Titanium Dioxide and Talc not Containing Asbestos or Asbestiform Fibers: Recent Evaluations by an IARC Monographs Working Group. *Inhalation Toxicology*, 19 (Suppl. 1): 213-228 (2007) and IARC Monographs on the Evaluation of the carcinogenic risk of chemicals to humans. Carbon black, Titanium dioxide, and Talc. Vol. 93, 477 p. (2010).

Summary of the meeting of the IARC working group in February 2006 that reconsidered the results of the meeting of 1983 (Vol. 42) and suppl. 1987

Summary	Significant risk				Level of proof				Remarks
	A	P	M*	C	Ab	L	I	H	
Italy, Rubino <i>et al.</i> , 1976, 1979		yes						x	Significant SMRs for miners with cumulative dose relationship in mppcf-years/effect.
			0	no		x			No data on smoking, insufficient exposure history. Methodological limitation.
Vermont, Selevan <i>et al.</i> , 1979 Miners Millers		no		yes		x			Small number, no mention of data on smoking. The latency for cancers seems to have not been taken into account.
		yes		no		x			Possibility of radon exposure.
Norway, Wergeland <i>et al.</i> , 1990		no	0	no		x			Small number in the cohort. High dust concentrations. Less than 1% quartz.
France, Wild <i>et al.</i> , 2000		yes				x			Pneumoconiosis: significant but based on three cases.
				no		x			Lung cancer: adjustment for smoking (partial information) and quartz, cumulative exposure to dust per individual. No fibre or EMP measurement. High dust exposure in the past. No increase in trend with the dose, but small number in some categories.
Austria, Wild <i>et al.</i> , 2002			0	no		x			Information on smoking not published. Small number.
France and Austria, Wild <i>et al.</i> , 2002			0	no			x		No increased cancer risk with increased dust exposure. Partial information for smoking. Adjustment for smoking, quartz and underground work.
Italy (Coggiola <i>et al.</i> , 2003)		yes	0	no			x		Update. NMRD found mainly in miners. No adjustment for smoking.
Québec (Ramanakumar, 2008)				no			x		Community-based case-control study. Weakness: estimate of exposure by experts. Strengths: histologically confirmed cancers, adjustments for smoking.

User industry									
USA, Thomas & Stewart, 1987 Manufacture of ceramic plumbing equipment				yes		x			Statistically significant in cases of exposure to high concentrations of respirable quartz. Accentuated by the presence of non-fibrous talc. Impossible to differentiate the causality of quartz and talc.
Conclusion ¹³		yes	0	no ¹⁴					Group 3: Inadequate evidence for the carcinogenicity of inhaled talc that does not contain either asbestos or asbestiform fibres.

A: NMRD, P: pneumoconiosis, M: mesothelioma, C: lung cancer, Ab: absent, L: low, I: intermediate, H: high;

*: indicates the number of observed cases of mesothelioma .

B1.3 Wild (2006)

The aim of the review by Wild was to update the epidemiological evidence on the carcinogenicity of talc not containing asbestiform fibres since the IARC evaluation in 1987 (Table B3). To do this, the author considered three studies in talc mines (Vermont, Norway and Italy) and four in mills (Norway, France, Austria and Italy) in addition to the results in seven talc-using industries. The tables by Wild that describe the characteristics of the exposed populations and the epidemiological data are reproduced in Appendix C.

Miners

Vermont cohort - Mine

Wild arrived at the same evaluation as the ATS, namely an increased significant risk of lung cancer in miners¹⁵ which did not appear in millers. The level of proof is “low” due to the lack of information on smoking, on exposure to other agents, as well as to the lack of a dose-response relationship. No follow-up could be identified in the literature searches.

Norwegian cohort - Mine

The Norwegian mine is described as possibly without quartz or radon (3.5 pCi/L) by Wild while Gamble and Gibbs (2008, page S168) mention traces of tremolite, quartz and anthophyllite (aspect ratio (L/d) > 3:1 by optical microscopy from 0.2 to 0.9 f/mL). Baan and Wild report no mesothelioma and no significant risk of lung cancer (SIR = 1.58 (0.18–5.69)). The number of workers in the cohort is small (n=94), which reduces the level of proof to “low.”

¹³ A Russian study (Katsnelson and Mokronosova, 1979) was not retained by the group of experts due to methodological limitations.

¹⁴ The group of experts classified talc in class 2B: possible human carcinogen by perineal route.

¹⁵ SMR data already indicated in the text are not repeated.

Italian cohort - Mine

In 2003, Coggiola *et al.* did a follow-up of the Italian cohort cited by the ATS (Rubino *et al.*, 1979). No mesothelioma was observed and the risk of lung cancer was non-significant (SMR = 1.07 (0.74–1.50)).

All miners

By combining the data on miners, Wild calculated a non-significant risk of lung cancer with a heterogeneity of the results caused by the high observed risk in Vermont miners, but the risk remained non-significant by calculating according to the fixed effects method (SMR = 1.20 (0.86–1.63) or randomly (SMR = 1.85 (0.68–5.05))).

Millers

Vermont cohort – Mill

Wild presented the same evaluation as the ATS, namely a non-significant risk of lung cancer with a lack of information on smoking and exposure.

Norwegian cohort – Mill

The Norwegian mill produces pure talc (see paragraph on the mine). The authors cited by Wild reported a non-significant risk of lung cancer (SIR: 2/1.27; 1.57 (0.19–5.69)), with a lack of information on smoking and lack of data on exposure, and therefore a “low” level of proof.

French cohort – Mill

The Luzenac mill processes an ore that contains less than 3% quartz without any identified carcinogen. Wild presented non-significant results of an increase in lung cancer (SMR = 1.24 (0.76–1.89)). A case-control study, nested in the cohort, did not indicate an increase in trend with the cumulative dose. The incomplete information on smoking tends towards an “intermediate” rather than “high” level of proof.

Austrian cohort – Mill and mine

The results of the study on the Austrian mills and mines come from two sites called B and C. The two locations gave SMRs of 0.69 (0.14–2.01) and 1.11 (0.01–6.19), but the number of cases (3 and 1) is very small. Smoking is only partially taken into account. The level of proof is established at “low.”

Italian cohort – Mill

The Italian mill produces talc without asbestiform fibres and less than 1% quartz. No mesothelioma was observed. The relative risk of lung cancer (SMR = 0.69 (0.34–1.23)) is less than 1. Smoking is only partially taken into account from personal communications on the workers and country’s populations. The level of proof is “intermediate”.

All millers

The entire population of millers that process an ore containing talc without asbestiform fibres leads to a risk evaluation (SMR = 0.92 (0.67–1.25)) of less than 1 with a level of proof that fluctuates between low and intermediate due to inadequate information on smoking and exposure.

Workers in user industries

Rubber

During the use of talc in a Chinese rubber industry, the authors cited by Wild observed a significant risk of lung cancer in males (RR = 3.3 (1.3–8.2)) with the same trend in female workers (RR: 4.6 (0.8–28.0)) after adjustment for smoking, but without adjustment for the other confounding agents, mainly curing agents, condensed volatile compounds, gases, and nitrosamines. No particulars are provided about the fibrous or non-fibrous nature of the dust. No exposure measurement is reported except the mention “working in the curing plant.” However, the authors favour a causal relationship with nitrosamine rather than with one of the other contaminants. In the absence of data on the confounding factors and on exposure, the level of proof is “low.”

In a German rubber industry where exposure to non-fibrous talc is evaluated as low/average/high from a semi-quantitative job-exposure matrix, the authors obtained a significant risk (RR = 2.4 (1.2–4.9)) which became non-significant (RR: 2.0 (0.9–4.1)) after adjustment for smoking and other unidentified agents. The level of proof is “low.”

Fibreglass

The article on an American fibreglass industry using talc did not give a significant risk of lung cancer (RR = 1.36 (0.41–4.52)) in a case (144) control (280) study after adjustment for smoking and the other exposures. The level of proof was evaluated as “low” due to these small numbers.

Paper

Two studies examined paper dust containing talc, one in a Norwegian pulp and paper industry and the other in two printing plants in Russia. In both articles, the risk of lung cancer was not significant (SIR = 1.4 (0.70–2.16) and SMR = 1.0 (0.35–2.18)). Smoking was not known and various other confounding agents were identified, namely SO₂, H₂S, Cl₂, ClO₂, benzene, solvents, aromatic hydrocarbons and carbon black.

Pottery (ceramics)

For workers always exposed to non-fibrous talc and to high concentrations of crystalline silica, the risk of lung cancer is RR = 2.54 (1.57–3.88). For workers exposed for 15 years or more to non-fibrous talc and to high concentrations of crystalline silica, this risk (RR = 3.64 (1.57–7.17)) increases with the number of years of exposure to non-fibrous talc, which is not observed with silica. The confounding effects of crystalline silica and fibrous talc cannot be completely

eliminated. However, no adjustment was done for smoking or for the other confounding factors, which is equivalent to a “low” level of proof.

Conclusion

Wild concluded that no mortality study indicated a significant increase in the risk of cancer in mills that process talc not containing asbestiform fibres. However, the level of proof remains intermediate due to the rarity of suitable information on exposure. In mines and user industries, where the talc may be accompanied by other carcinogens, the risk of lung cancer remained possible in a few articles, but a causal link is difficult to establish due to the deficiencies in exposure data.

Table B3: Analytical grid – Reviews – Lung cancer Wild (2006)

P. Wild. Occup. Environ. Med., Jan. 2006; 63 4-9. Lung cancer risk and talc not containing asbestiform fibres: a review of the epidemiological evidence.

Aim: To update the evidence on the carcinogenicity of talc not containing asbestiform fibres since the evaluation by IARC in 1987. The forms of fibrous talc (WHO) but non-asbestiform talc represent less than 1% of the powder at the output of the mill.

Summary	Significant risk				Level of proof				Remarks
	A	P	M*	C	Ab	L	I	H	
Mines									
Vermont (Selevan <i>et al.</i> , 1979)				Possible		x			Exposure to radon and quartz. Methodological difficulties: unknown smoking and inadequate data on exposure.
Norway (Wergeland <i>et al.</i> , 1990) Morbidity and mortality in talc-exposed workers			0	no		x			Small number (94 workers/2 cases).
Italy (Coggiola <i>et al.</i> , 2003) An up-date mortality study of talc miners and millers in Italy			0	no		x			High quartz exposure in the past. Relationship to the dose.
All miners				no		x			Heterogeneity due to risk from Vermont which is much greater.
Mills									
Vermont (Selevan <i>et al.</i> , 1979)			0			x			Unknown smoking and inadequate exposure data.
Norway (Wergeland <i>et al.</i> , 1990)			0	no		x			Small number (295 workers/4 cases). Very pure talc.
France (Wild <i>et al.</i> , 2002)				no			x		No fibre measurement. Dust measurements. High dust exposure in the past. No increase in trend with the dose. Partial management of smoking.
Austria (Wild <i>et al.</i> , 2002)	B			no		x			Very small number (40 and 11). Information on exposure and on the sites difficult to interpret.
C				no		x			
Italy (Coggiola <i>et al.</i> , 2003)			0	no			x		Very limited data on exposure. Fragmentary information on smoking.
All millers				no			x		No increased risk of lung cancer in millers.

User industries									
Zhang <i>et al.</i> (1989)				yes**		x			Shanghai rubber plant. No particulars on fibrous or non-fibrous nature. Other: curing agent, condensed volatiles, gases, nitrosamines. Adjustment for smoking. No exposure data except "working in a curing plant." No adjustment for the other confounding agents.
Chiazze <i>et al.</i> (1993)				no		x			Fibreglass plant. Talc exposure expressed in estimated f/mL. Known smoking. Other contaminants: asbestos, silica, formaldehyde.
Straif <i>et al.</i> (1999)				yes		x			German rubber plant. Exposure: low/average/high to non-fibrous talc. Without adjustment for high talc exposure. Confounding factors: asbestos and nitrosamines.
Straif <i>et al.</i> (2000)				no		x			Adjustment for smoking and other unidentified agents RR: 2.0 (0.9–4.1)
Langseth and Andersen (1999)				no		x			Paper dust containing talc. Other contaminants: SO ₂ , H ₂ S, Cl ₂ , ClO ₂ No information on smoking.
Bulbulyan <i>et al.</i> (1999)				no		x			Printing plant. Paper dust containing talc. Other contaminants: Benzene, solvents, aromatic hydrocarbons and carbon black. No information on smoking.
Thomas, T.L. <i>et al.</i> (1987, 1990)				yes			x		Pottery. Risk increases with the number of years of exposure to non-fibrous talc, which is not observed with silica. The confounding effects of crystalline silica and fibrous talc cannot be completely eliminated.
Conclusion									
Mill				no			x		No mortality studies that indicate an increase in cancer risk. None of the cited studies characterized the non-asbestiform fibres.
Talc + other carcinogens including mines and user industries.				Possible		x			Few studies with appropriate information on exposure.

A: NMRD, P: pneumoconiosis, M: mesothelioma, C: lung cancer, Ab: absent, L: low, I: intermediate, H: high

*: indicates the number of observed cases of mesothelioma;

**: in males.

Appendix B2. Scientific articles

B2.1 Gibbs *et al.* (1992)

The aims of the article by Gibbs *et al.* (Table B4) were to confirm the existence of talcosis as a distinct lung disease and to observe a relationship between exposure and pulmonary retention as determined by the mineralogic analysis of the tissues of 17 cases, most of which came from autopsy at death caused by or associated with pulmonary fibrosis. The results support the diagnosis of “talcosis” in most of the workers with a few cases with a preponderance of mica rather than talc. Asbestos is present only at low concentration in 6 cases ($1-16 \times 10^6$ fibres/g of lung tissue; tremolite: 2 cases, amosite: 1 case, and chrysotile: 3 cases) while fibrous particles other than asbestos, according to the WHO definition, varied from $1-538$ fibres $\times 10^6$ fibres/g. The authors point out the usefulness of mineralogic analysis for substantiating a diagnosis. They stress that the results support the existence of talcosis in workers working with talc containing almost no tremolite, but that the causal link must be shared with different minerals.

Table B4: Analytical grid – Articles – Gibbs *et al.* (1992)

A. E. Gibbs, F. D. Pooley, D. M. Griffiths, R. Mitha, J. E. Craighead, and J. R. Ruttner. Talc pneumoconiosis: a pathologic and mineralogic study. *Hum Pathol* 23 (12):1344-1354, 1992.

Aims: To confirm the existence of talcosis, to compare primary, secondary and tertiary exposures, to observe a relationship between exposure and pulmonary retention. Pathologic and mineralogic examination of 17 cases of “talc pneumoconioses” or talcosis.

Summary	Significant risk				Level of proof				Remarks
	A	P	M	C	Ab	L	I	H	
		yes				x			Shared causality between a variety of minerals. Supports the existence of talcosis in workers working with talc containing almost no tremolite.

A: NMRD, P: pneumoconiosis, M: mesothelioma, C: lung cancer, Ab: absent, L: low, I: intermediate, H: high

B2.2 Gamble (1993)

This article was cited and discussed by the ATS (Table B1) with the mention “not published.” It is presented in Table B5 for purposes of thoroughness. It is a case-control study nested in a cohort whose purpose was to evaluate the potential effect of exposure measured by the number of years on the job and the confounding factors, such as smoking. The 22 cases and 66 controls were paired according to date of birth and date of hiring. The cases were all smokers (91%) or former smokers (9%) compared to the controls who were 64% smokers, 9% former smokers, and 27% non-smokers. Risk trends, which were significant in the previous studies, had a negative slope, by correcting for smoking, for a duration of exposure longer than 20 years, and for the elimination of workers with less than one year of experience. The authors concluded that there was a risk of lung cancer linked to smoking rather than to talc ore dust exposure factors.

Table B5: Analytical grid – Articles – Gamble (1993)

J. F. Gamble. A nested case control study of lung cancer among New York talc workers. *Int Arch Occup Environ Health*. 64 (6):449-456, 1993.

Investigation of confounding factors. Cumulative exposure to be published.

Summary	Significant risk				Level of proof				Remarks
	A	P	M	C	Ab	L	I	H	
				no		x			Increased risk with number of years on the job which acquires a negative slope after adjustment for smoking. No dose-exposure relationship. More congruent results with an etiology to tobacco rather than talc.

A: NMRD, P: pneumoconiosis, M: mesothelioma, C: lung cancer, Ab: absent, L: low, I: intermediate, H: high

B2.3 Hull et al. (2002)

In a short article, Hull *et al.* (Table B6) reported 5 new cases of mesothelioma in Jefferson and St. Lawrence counties in New York State, which they believed would bring to 8 the number of identified cases in the state. However, the article does not contain any description of the occupational history. The mineralogic analysis indicates the similarity in pulmonary burden of cases and controls. This article's content was contested by Gamble and Gibbs and by Price, in section B.3 "Other publications."

Table B6: Analytical grid – Articles – Hull et al. (2002)

M. J. Hull, J. L. Abraham and B. W. Case. Mesothelioma among workers in asbestiform fiber bearing talc mines in New York State. *Ann. Occup. Hyg.*, Vol. 46, Supplement 1, pp. 132–135, 2002

Reports 5 new cases of mesothelioma in Jefferson and St. Lawrence counties in New York State. Indicates the similarity in pulmonary burden between cases and controls.

Summary	Significant risk				Level of proof				Remarks
	A	P	M*	C	Ab	L	I	H	
			5			x			Reporting of cases (5) without risk assessment except an increase in increasing trend in the number of deaths by mesothelioma in the counties between 1950 and 1997. No mention of occupational history.

A: NMRD, P: pneumoconiosis, M: mesothelioma, C: lung cancer, Ab: absent, L: low, I: intermediate, H: high

*:Indicates the number of observed cases of mesothelioma

B2.4 Roggli et al. (2002)

Roggli *et al.* (Table B7) present the results of mineralogic analyses of the pulmonary retention of fibres for 312 cases of mesothelioma. Scanning electron microscopy was used. Of the 312 cases, 166 contained tremolite with 81 above background levels; for 193 cases, fibrous talc was identified; and 32 cases involved chrysotile. The occupational history of the cases that had tremolite results higher than the

background level, when it was known (70/81), involved the group of users of products containing asbestos or by-standers of end-users. The authors conclude, among other things, that the data were consistent with the pulmonary burden rate for tremolite that comes from talc and from chrysotile, and that the results do not support the assumption that tremolite is removed during the milling process.

Table B7: Analytical grid – Articles – Roggli *et al.* (2002)

V.L. Roggli, R.T. Vollmer, K.J. Butnor and T.A. Sporn. Tremolite and Mesothelioma. Ann. Occup. Hyg. 46 :447-453(2002).									
Analysis of the lung fibre burden of 312 cases of mesothelioma.									
Summary	Significant risk				Level of proof				Remarks
	A	P	M	C	Ab	L	I	H	Seems to indicate that tremolite from chrysotile and talc could be the causal agent and that tremolite is not removed during milling.
			Yes*			x			

A: NMRD, P: pneumoconiosis, M: mesothelioma, C: lung cancer, Ab: absent, L: low, I: intermediate, H: high

*: mineralogic study of 312 cases of mesothelioma, 193 of which showed the presence of talc.

B2.5 Honda *et al.* (2002)

Honda *et al.* reported the follow-up until 1989 of the mortality studies (Table B8) cited by the ATS (Table B1) on industrial class tremolitic talc from mines and mills in upstate New York. They obtained significant SMRs (232 (157–329)) for lung cancer and for NMRD (221 (147–320)) for all of the workers. Cases of lung cancer were concentrated in miners (394 (233–622)) and became non-significant in millers (128 (51–223)), while the excess NMRD remained constant in both groups. Respirable dust was sampled and measured for all the jobs without specification of composition. The authors were unable to adjust for smoking and other confounding factors, due to a lack of information. No relationship was observed between the dose and the lung cancer risk, but there is a dose-effect relationship for fibroses between those weakly and strongly exposed. The authors concluded that there is a relationship to talc ore dust exposure for NMRD (non-malignant respiratory disease). The level of proof was limited to intermediate, due to inadequate information about the exposure and confounding factors. However, the authors did not conclude that this relationship existed for excess lung cancer, even though it was significant. One of the hypotheses that would explain the cancer results would be the presence of a contaminant whose concentration would not be related to the respirable dust results.

Table B8: Analytical grid – Articles – Honda (2002)

Y. Honda, C. Beall, E. Delzell, K. Oestenstad, I. Brill and R. Matthews. Mortality among Workers at a Talc Mining and Milling Facility Ann. Occup. Hyg. **46**(7)575-585, 2002

Mortality study. Follow-up until 1989 of the studies reported by the ATS. Industrial class tremolitic talc from mines and mills in upstate New York.

Summary	Significant risk				Level of proof				Remarks
	A	P	M	C	Ab	L	I	H	
				no		x			Only respirable dust is sampled and measured without specification of the composition. Significant SMR in miners only. No adjustment for smoking and other confounding factors. No relationship between the dose and risk of lung cancer, but a dose-effect relationship between those with low and high exposure for fibroses. Concluded that there is a relationship with talc exposure for NMRD but not for excess cancer even though it was significant.
		yes					x		

A: NMRD, P: pneumoconiosis, M: mesothelioma, C: lung cancer, Ab: absent, L: low, I: intermediate, H: high

B2.6 Ramanakumar et al. (2008)

In the databases of two large population-based case-control studies on lung cancer in the Montréal region, Ramanakumar *et al.* (Table B9) were able to extract two sub-populations of subjects exposed during their lifetime to talc used for industrial or cosmetic purposes. The results of the case-control study showed no excess risk of lung cancer in the exposed subjects after adjustment for smoking and several other confounding factors. The tables taken from the article summarize the exposure results (Table B10) and the odds ratio (OR) (Table B11). The authors emphasize, among the limitations of their study, the small number of workers exposed to high concentrations and the fact that there are more users than miners or millers. The ORs were adjusted for age, family income, ethnicity, the respondents' status, educational level, smoking in three variables, and at least one of the three workplace carcinogens (asbestos, crystalline silica and cadmium compounds).

Table B9: Analytical grid – tremolitic talc – Ramanakumar *et al.* (2008)

A. V. Ramanakumar, M.-É. Parent, B. Latreille and J. Siemiatycki. Risk of lung cancer following exposure to carbon black, titanium dioxide and talc: Results from two case-control studies. <i>Int. J. Cancer</i> . 122 : 183-189 (2008).									
Groups of experts evaluated the exposure from the occupational history. Talc source undetermined except industrial (undetermined presence of cleavage fragments or asbestiform or non-asbestiform fibres) and cosmetic talc (without contaminant).									
Summary		Significant risk			Level of proof				Remarks
	A	P	M	C	Ab	L	I	H	Small number of workers exposed to high concentrations. More talc users than producers.
				no			x		

A: NMRD, P: pneumoconiosis, M: mesothelioma, C: lung cancer, Ab: absent, L: low, I: intermediate, H: high

**Table B10: Prevalence of lifetime exposure to talc
(adapted from Table III from Ramanakumar *et al.*, 2008)**

Exposure	Industrial talc		Cosmetic talc	
	n ¹	%	N ¹	%
All subjects	5847	100.0	5847	100.0
Exposed	267	4.9	194	3.5
Confidence level				
Possible	70	1.3	38	0.7
Probable	95	1.7	66	1.2
Certain	102	1.9	90	1.6
Frequency				
< 5%	34	0.8	49	0.9
5–30%	190	3.4	140	2.5
>30%	43	0.7	5	0.1
Concentration				
Low	213	3.9	136	2.5
Medium	54	1.0	58	1.0
High	0	0	0	0
Duration				
1–10 years	110	2.0	90	1.6
11–20 years	58	1.1	44	0.8
>20 years	99	1.8	60	1.1

¹n and N: The difference between the two ways of expressing the number of cases is not indicated in the article

Table B11: Odds ratios (OR) for lung cancer following talc exposure
(adapted from Table IV from Ramanakumar *et al.* (2008))

No exposure	Ca/Co ¹	OR (95% CI ²)
Industrial talc		
No exposure	67/127	1.0 (0.6–1.5)
Unsubstantial exposure	49/92	1.0 (0.7–1.4)
Substantial	18/35	0.9 (0.6–1.8)
Cosmetic talc		
No exposure	53/98	0.9 (0.5–1.3)
Unsubstantial exposure	47/74	1.0 (0.7–1.5)
Substantial	6/24	0.7 (0.3–1.8)

¹The significance of Ca/Co is not indicated in the text; it is probably cases and controls

²Confidence interval

B2.7 Wild *et al.* (2008)

The aim of Wild *et al.* (Table B12) was to examine the effects on the respiratory health of 378 talc workers, French and Austrian, exposed to respirable dust from talc ore without asbestos fibres, at a concentration equal to or less than 2 mg/m³. These workers were monitored by means of a chest X-ray, spirometry and a standardized questionnaire. Of the 438 participants, 378 were examined at least twice. The inclusion criteria accepted all workers who had worked for 5 consecutive years between 1988 and 2003. The prevalence of small radiological opacities and reduction in respiratory functions was significantly related to cumulative exposure at inclusion but was not related to the exposure during the period of the study. The exposures were evaluated from a job-respirable dust exposure matrix. The authors concluded that “even if early exposure levels to talc as assessed at inclusion was associated with a reduction in lung function and increased prevalence of small radiological opacities, there was no evidence of detrimental effects of talc exposure, as determined during the study period, on lung function and small radiological opacities.”

Table B12: Analytical grid – Articles – Wild *et al.* (2008)

P. Wild, K. Leodolter, M. Réfrégier, H. Schmidt and E. Bourgkard, Effects of talc dust on respiratory health: results of a longitudinal survey of 378 French and Austrian talc workers. *Occup. Environ. Med.* **65**:261-267(2008).

Aim: To examine the respiratory health effects of the dust of talc ore without asbestos fibres, at a concentration equal to or less than 2 mg/m³.

Summary	Significant risk				Level of proof				Remarks
	A	P	M	C	Ab	L	I	H	
	no						x		Statistically significant reduction in lung function and increase in the prevalence of small lung opacities at inclusion. No evidence of adverse effects following exposure to talc dust during the 14.5 years of the study.

A: NMRD, P: pneumoconiosis, M: mesothelioma, C: lung cancer, Ab: absent, L: low, I: intermediate, H: high

Appendix B3. Other publications

B3.1 OSHA (1992)

In the United States, in general, OSHA arrives at its decisions on regulations by establishing a proposal following the study of available scientific knowledge, by discussing this proposal during expert hearings and testimony from individuals or organizations, and finally, by drafting OSHA's final position. In its final position, which deals with talc, among other things, OSHA discusses the specific case of the talc mine and mill in New York State. With the controversy on the identification of the mineral components of this mine and despite the studies and presentations of NIOSH which supports the excess cancer caused by exposure, OSHA concluded that there was insufficient data to come to a conclusion on the causality of the non-asbestiform components and that there was no need to regulate them in the absence of proof. While recognizing that exposure in the mine may cause respiratory diseases, particularly benign respiratory diseases, there are no data that allow a conclusion on the causality of the non-asbestiform forms of anthophyllite, tremolite and actinolite (ATA). According to OSHA, with this state of knowledge, any risk assessment, qualitative or quantitative, is impossible. To our knowledge, this position by OSHA has not been modified since that time.

B3.2 Guthrie (1992)

Guthrie presented a review of the biological effects of ores whose dust can be inhaled by workers. All the references have already been cited by the ATS, except the article by Cullinan and McDonald (1990) that reported, in the proceedings of a conference, the grouping of seven studies, three with "pure" talc where there was no excess risk of lung cancer, and four, all in the New York mine, with talc contaminated by mineral fibres, where there is a risk of lung cancer and mesothelioma (0 to 2 cases). Cullinan and MacDonald concluded that it is improbable that talc not containing mineral fibres is the cause of lung cancer or mesothelioma but that new studies would be necessary to confirm it. Guthrie associates the miners and millers in New England with articles by Brown and Wagoner (1980) and by Leophonte and Didier (1990), which seems incorrect to us.

B3.3 Ilgren (2004)

Beginning with the introduction, the author indicated that he collected all the evidence that demonstrates that "the toxicity of respirable cleavage fragments is so much less than that of the fibrous amphiboles that by any reasonable measure they are not biologically harmful." In addition to the 141 references, the article refers to 24 unpublished references by Addison, and 20 "personal communications" from 10 scientists.

In the section on epidemiology entitled "Epidemiological Studies Show No Association Between Exposure to Amphibole Cleavage Fragments and Asbestos-Related Disease," the author presents six examples related to the extraction, production or use of talc, namely: talc miners in the New York State Gouverneur Talc Company (GTC), workers in the American paint plant exposed to GTC talc, ceramics pottery workers, Norwegian miners and millers, Italian miners and millers, and Vermont miners and millers.

In his conclusion on the epidemiological aspect, the author writes that “Epidemiological studies of many tens of thousands of workers in various primary and secondary industries exposed to cleavage fragments fail to reveal evidence of an attributable cancer excess.”¹⁶

B3.4 Gamble and Gibbs (2008)

Gamble and Gibbs described their procedure as an external risk comparison. The aim of the study was to compare, as much as possible, the risks of cancers (lung cancer and mesothelioma) of workers exposed to the cleavage fragments of airborne amphiboles and those of workers exposed to analogue amphiboles that form asbestos fibres.¹⁷

To do this, the authors compared the risks of lung cancer and mesothelioma of populations of workers:

- In the talc deposits (New York and Norway) that contain anthophyllite, tremolite and non-asbestiform transition ores, from the Homestake gold mine and the taconite (iron) mine that contain grunerite (non-asbestiform amphiboles);
- From the mines, mills and industries using amosite, from the anthophyllite mines (positive control);
- Exposed to talc not containing amphiboles in Vermont, Italy, France and Austria (negative control).

Mortality from lung cancer is then analyzed in relation to the exposures by number of asbestos fibres and cleavage fragments. Finally, the risks of lung cancer and mesothelioma from mines whose ore contains amphibole cleavage fragments are compared to ores that do not contain either asbestos or amphibole cleavage fragments. This latter procedure is equivalent to the procedure of Wild (Table B3).

Gamble and Gibbs summarized the results of different studies on talc mines. This presentation has the advantage of reporting NMRD from several cohorts of miners and millers. The mines in New York (significant SMR between 2.21 and 2.88), in Vermont (11/3.67, SMR = 3.0 (1.50–5.36)), and Italy (127/55.7, SMR = 2.28 (1.9–2.72)) present a statistically significant increase in NMRD, while France, Austria and Norway do not reach the level of significance. The authors use these results to confirm that dust exposure in France and Austria is relatively low, but cannot explain the results in Norway where the exposure measurements are very high.

Table B13 gives a historical follow-up on the evolution in knowledge at the New York talc mine, which is a mine whose ore containing asbestos and/or cleavage fragments has been the subject of many studies. Knowledge about the nature of the exposure in this mine has also evolved over the years (see Table 3) and is still the subject of discussion (NIOSH, 2010).

¹⁶ To support this statement, reference #15 of the article is entitled: Controls of amphibole formation in chrysotile deposits: evidence from the Jeffrey Mine. Williams-Jones A, Normand C, Clark J, Vali H, Martin, R. Asbestos, Quebec, Can. Min. (Spec. Pub. 5) 2001;89-104.

¹⁷ In this section, we extracted, from the analysis by Gamble and Gibbs, only the epidemiological information that involved cleavage fragments in talc.

Table B13: Summary of results for lung cancer and mesothelioma from studies of NY talc workers

Reference	Study characteristics	Lung cancer	Mesothelioma
Kleinfeld <i>et al.</i> (1967)	220 NY Talc Miners ≥ 15 years tenure in 1940; 1965 follow-up, 91 total deaths, PMR	PMR = 3.44 (1.65–6.3) (11 deaths)	1 peritoneal mesothelioma (1.1%)
Kleinfeld <i>et al.</i> (1974)	260 NY Talc Workers ≥ 15 years in 1940 or between 1940 and 1969; 108 total deaths, PMR, follow-up of Kleinfeld <i>et al.</i> (1967)	PMR resp cancer = 3.24 (1.72–5.54) (12 lung cancer, 1 fibrosarcoma of pleura)	1 peritoneal mesothelioma (0.93%)
Brown <i>et al.</i> (1979, 1980)	398 WM employed GTC 1947–1959, follow-up 1975; 18% <1 month, 24% 1–6 months, 50% <1 year; 44% <1950;	9/3.3 = 2.73 (1.25–5.18) ($p < 0.05$); 4 <1-year tenure	1/74 = 1.4% (16-year talc tenure, 11 years construction)
Stille and Tabershaw (1982)	655 WM employed GTC 1948–1978, vital status 1978;	10/6.4 = 1.57 (10 obs) Prior employment = 2.14 (8 obs) No prior work = 0.76 (2 obs)	
Lamm <i>et al.</i> (1988)	705 men employed GTC 1947–end 1977, vital status 1978	12/5 = 2.40 (1.24–4.19) >1 year 6/3.1 = 1.93 (0.71–4.20) prior risk = 3.08 (6/2) <1 year 6/1.9 = 3.16 (0.16–6.88) prior risk = 3.33 (3/0.9)	1 electrician 15-year latency; 20-years prior As miner, miller, construction
Brown <i>et al.</i> (1990)	710 WM employed at GTC 1947–1978 with vital status 1983; Not reported	17/8.2 = 2.07 (1.20–3.31) <1-year = 3.64 (1.54–7.04) 1–9 years = 0.83 (0.02–4.57) 10–19 years = 4.0 (0.54–16.1) 20–36 years = 1.82 (0.21–6.36)	
Gamble (1993)	22 lung cancer cases at GTC 1947–1978 matched 3:1 on data of birth and date of hire	OR lung cancer Tenure smokers >20-year latency <5 year 1.0 5–15 years 0.63 15–36 years 0.42	
Honda <i>et al.</i> (2002)	809 WM talc workers employed GTC 1948–1989 follow-up Cancer: 1950–1989 Non-cancer mortality = 1960–1989	mg/m ³ days RR (n) <95 1.0 (11) <987 0.8 (9) 987 + 0.5 (9) Hired: <1955 SMR 2.86 (0.9–4.1) Hired > 1955 SMR: 0. (0.2–2.4)	Two cases not considered causal due to short latency, Case 1 & Very low exposure, Case 2 (3.7%)

All but two of the studies (Kleinfeld *et al.*, 1967, 1974) were the same cohort of GTC workers.

Pn, pneumoconiosis; PMR: Proportional mortality ratio

Reproduced from Gamble and Gibbs (2008). Table A2, p. S182.

In the presentation of Gamble and Gibbs (2008), the Norwegian talc mine and mill are included in the category of ores that contain traces of quartz, anthophyllite and tremolite, but the small numbers of workers (94 miners and 295 millers) do not allow a definitive conclusion to be reached about the fact that no significant risk was observed for NMRD and lung cancer. No mesothelioma was reported. The absence of significant risk for NMRD is inexplicable due to the high exposure to dusts which should produce significant risk compared to the other talc mines and mills.

The authors continued their analysis by describing mines and mills whose talc ore does not contain amphibole, in Italy, France and Austria. The results, summarized in Figure 1, do not present any increase in significant risk, which brings Gamble and Gibbs to **conclude that “pure” talc does not cause an increase in lung cancer or mesothelioma.**

For the authors, the results in the New York and Vermont mines and mills are still unexplainable. In addition, Gamble and Gibbs contest the attribution of mesotheliomas caused by talc ore dust in the publication of Hull *et al.* (2002) because:

- Work history is unknown;
- Mineralogic analysis of pulmonary retention on two cases, insufficient;
- The dimension of the fibres in these two cases correspond to asbestos exposure;
- In all likelihood, the dimensions of the fibres retained in the lung do not correspond to the size of fibres in the New York talc mine;
- In the cohorts, the population of workers and the exposure are well described and no association was observed between talc or asbestiform amphiboles and mesothelioma in the absence of possible exposure to asbestos. The article by Hull is equivalent to a case history;
- The vermiculite cohort of Libby clearly indicated a risk of mesothelioma caused by asbestiform tremolite without a link to exposure to non-asbestiform tremolite.

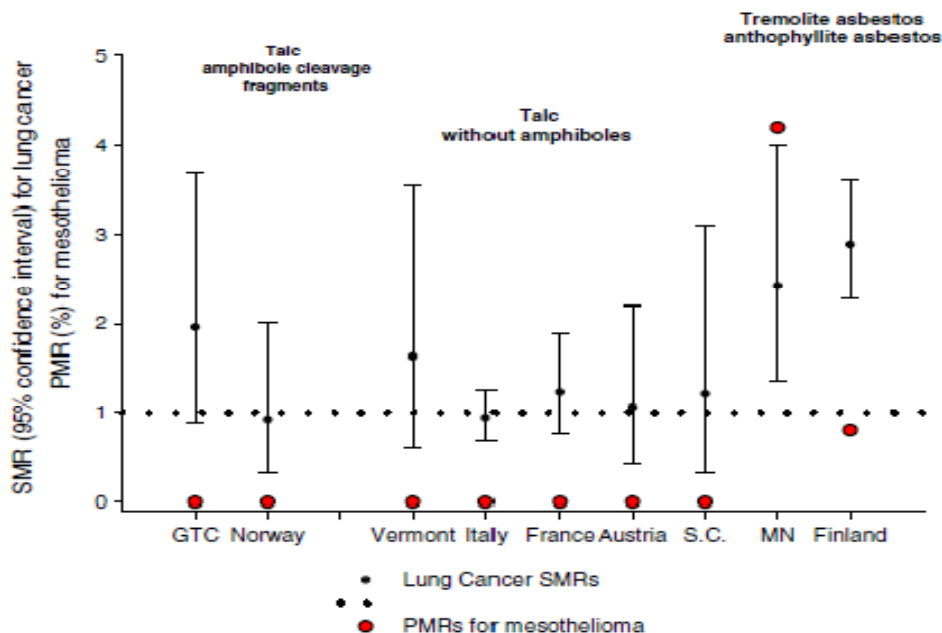


Fig. 6. Lung cancer and mesothelioma mortality in workers exposed to Talc containing non-asbestiform amphiboles in New York and Norway (Honda et al., 2002, Wergeland et al. (1990) Talc without amphiboles (Vermont, Italy, France/Austria) Selevan et al. (1979), Coggiola et al. (2003), Wild et al. (2002) and Vermiculite containing tremolite asbestos McDonald et al., 1986a,b Anthophyllite Asbestos (Karjalainen et al., 1994; Meurman et al., 1994).

From Gamble and Gibbs (2008) page S175

Figure 1: Lung cancer and mesothelioma mortality in workers in New York State and Norway

B3.5 Price (2010)

The aim of the article by Price was to show that amphibole asbestos has been incorrectly identified by public organizations and that the causal relationship between New York talc and mesotheliomas is incorrect. The author did a follow-up of the cohort of Honda *et al.* (2002) (RTV's Gouverneur mine, NY) from 1989 to 2008. He argued that the two cases of mesothelioma reported by Honda are doubtful diagnoses as well as unrelated to talc exposure. As for the five cases of mesothelioma reported by Hull *et al.* (2002), he indicated that one case refers to a miner active for a short period, and that following an expert assessment (Dr. E. Rubin), the four other cases are claims whose diagnosis is questionable. In summary, the RTV Gouverneur cohort seems to involve only one mesothelioma instead of the eight reported by Honda and Hull. The PMR would therefore be 0.17, which is ten times smaller than the asbestos mines with amphibole exposure and too small to substantiate a causal link with RTV talc exposure.

APPENDIX C: TABLES TAKEN FROM WILD *ET AL.* (2006)¹⁸

¹⁸ Downloaded from oem.bmj.com on June 9, 2010

Table C1: Summary characteristics of talc exposed populations in talc producing companies**Table 1** Summary characteristics of talc exposed populations in talc producing companies

Study	Cohort definition	Talc exposure	Other	Smoking
Selevan <i>et al</i> , talc miners ⁴	All male talc miners radiographed in annual surveys of workers in dusty trade in Vermont (US), from five companies with at least one year employment between 1940 and 1969, followed up from 1940–75	No information Levels >20 mppcf not uncommon	Radon (up to 1.2 WL = 240 pCi/l), possibly tremolite	No information
Selevan <i>et al</i> , talc millers ⁴	All male talc millers radiographed in annual surveys of workers in dusty trade in Vermont (US), from five companies with at least one year employment between 1940 and 1969, followed up from 1940–75	No information Levels >20 mppcf not uncommon	None, quartz <0.25%	No information
Wergeland <i>et al</i> , talc miners ¹⁵	All male employees from a Norwegian mine with at least one year employment between 1944 and 1972 followed up from 1953–87	In 1980: 0.94–97.35 mg/m ³ peak at 319 mg/m ³ 0.2–0.9 f/ml	3.5 pCi/l radon	76% smokers in 1981
Wergeland <i>et al</i> , talc millers ¹⁵	All male employees from a Norwegian talc mill with at least two years employment between 1935 and 1972 followed up from 1953–87	In 1980: 1.4–54.1 mg/m ³ peak at 109 mg/m ³ 0.2–0.9 f/ml	None	No information
Wild <i>et al</i> , French talc millers ²¹	All male employees from a French talc mill (site A) with at least one year employment between 1945 and 1994 followed up from 1968–95	>30 mg/m ³ in production until the 1970s, 5–30 mg/m ³ until 1990, <5 mg/m ³ since except some dusty jobs	None, quartz <3%. Some workers had past quartz exposure in former jobs	59% present smokers in 1989; 39% in a French population survey in 1986
Wild <i>et al</i> , Austrian talc millers and miners ²¹	All male workers of an Austrian talc producing company having been employed at least one year in three mines (site B to D) and mills or in the head office (site E) between 1972 and 1995 followed up from 1972–95.	>30 mg/m ³ in sites B and C before 1960 and for millers in D 1970–80, 5–30 for millers 1960–80, <5 since 1980	Quartz (and no talc) in site D and in miners of site B until 1960 Elsewhere quartz <3%	42% smokers in 1988; 16% ex-smokers in site B
Coggiola <i>et al</i> , Italian talc miners ²²	All male employees from Italian talc mine with at least one year employment between 1946 and 1995 followed up from 1946–95	Decreased from more than 200 mppcf in 1950 to less than 5 mppcf in 1965 (Rubino 1979)	High quartz in the past. Radon in 1992, 500 Bq/m ³ = 13.5 pCi/l	47% smokers in 1993; 34% in an adult Italian population survey in 1994
Coggiola <i>et al</i> , Italian talc millers ²²	All male employees from Italian talc mill with at least one year employment between 1946 and 1995 followed up from 1946–95	Decreased from about 20 mppcf until 1960 to about 5 mppcf in 1975 (Rubino 1979). In 1993 1.3 mg/m ³ (personal communication)	None Quartz <1%	44% smokers in 1993; 34% in an adult Italian population survey in 1994

Table C2: Summary characteristics of talc exposed populations in other industries**Table 2** Summary characteristics of talc exposed populations in other industries

	Cohort definition	Talc exposure	Other	Smoking
Thomas <i>et al</i> , pottery workers ^{12, 13}	All employees of three US ceramic factories with one year employment 1939–66 followed up from 1955–81	No, non-fibrous, fibrous	Quartz high/low	No information
Zhang <i>et al</i> , rubber workers ¹⁴	Employees (male and female) of a Shanghai rubber factory who entered a screening program for heart disease in 1972 followed up from 1972–84	Exposure during curing. No precision as to whether fibrous or not fibrous	Curing agents, condensed volatiles, gases, nitrosamines	Available for everybody, controlled in the analysis
Chiazze <i>et al</i> , fibreglass workers ¹⁶	Production and maintenance workers employed at least one year in a Ohio fibreglass plant from 1940–62, followed up until 1982	Expressed in estimated f/ml. No precision as to whether fibrous or not fibrous	Asbestos, silica, formaldehyde,	Available for everybody, controlled in the analysis
Straif <i>et al</i> , rubber workers ^{17, 18}	All male employees from five German rubber plants with at least one year employment retired or active in 1981 followed up from 1981–91	Low/medium/high Non-fibrous talc	Asbestos, nitrosamines, carbon black	No information
Langseth and Andersen, paper workers ²⁰	All female employees of a pulp and paper mill working at least one year between 1920–93 followed up for cancer incidence from 1953–93	As a constituent of paper dust in the paper departments	Paper dust, sulphur dioxide, hydrogen sulphide, chlorine, chlorine dioxide	No information
Bulbulyan <i>et al</i> , printing workers ¹⁹	All female employees of two printing plants working at least two year between 1978–93 followed up for cancer incidence from 1979–93	As a constituent of paper dust in the book binding department and among press operators	Paper dust, benzene, solvents, aromatic hydrocarbons, carbon black	No information

Table C3: Lung cancer and mortality from all causes in the talc producing companies**Table 3** Lung cancer and mortality from all causes in the talc producing companies

	n	Lung cancer Type of RR	RR (cases)	95% CI	Mortality, all causes SMR (cases)
Talc millers					
Vermont ⁴	225	SMR US rates	1.02 (2)	0.09–3.69	1.18 (44)
Norway ¹⁵	295	SIR Norwegian rates	0.77 (4)	0.21–1.96	0.74 (90)
Italy ²²	551	SMR regional rates	0.69 (11)	0.34–1.23	1.08 (290)
France ²¹	945	SMR regional rates	1.24 (21)	0.76–1.89	0.93 (294)
Austria, site B		SMR regional rates	0.69 (3)	0.14–2.01	0.70 (40)
Austria, site C		SMR regional rates	1.11 (1)	0.01–6.19	0.97 (11)
All talc millers—fixed effect			0.92 (42)	0.67–1.25	0.95 (769)
Talc miners					
Vermont ⁴	163	SMR US rates	4.35 (5)	1.40–10.2	1.28 (34)
Norway ¹⁵	94	SIR Norwegian rates	1.58 (2)	0.18–5.69	0.82 (27)
Italy ²²	1244	SMR regional rates	1.07 (33)	0.74–1.50	1.26 (590)
All talc miners—fixed effect			1.20 (40)	0.86–1.63	1.24 (651)
All talc miners—random effect			1.85 (40)	0.68–5.05	1.10 (651)

RR, relative risk; SIR, standardised incidence ratio; SMR, standardised mortality ratio.

Table C4: Lung cancer relative risks in relation to talc exposure in other industries**Table 4** Lung cancer relative risks in relation to talc exposure in other industries

	n	Lung cancer	RR (exposed cases)	95% CI
		Type of relative risk		
Ceramic industry, US ^{12 13}	2055	SMR ever exposed to non-fibrous talc and high silica (US rates)—unadjusted	2.54 (21)	1.57–3.88
		SMR exposed to 15+ years non-fibrous talc and high silica (US rates)—unadjusted	3.64 (8)	1.57–7.17
Rubber industry, China ¹⁴	1624	Mantel-Haenszel RR (rubber curing adjusted on smoking)	Males 3.3 (7) Females 4.6 (2)	1.3–8.2 0.8–28.0
Rubber industry, Germany ^{17 18}	8933	Internal RR (high talc exposure unadjusted)	2.4 (13)	1.2–4.9
		Internal RR (high talc or asbestos exposure adjusted on smoking and other exposures)	2.0 (13)	0.9–4.1
Glass fibre production, US ¹⁶	144 cases, 280 controls	OR (high talc exposure adjusted on smoking and other exposures)	1.36 (10)	0.41–4.52
Printing industry, Russia ¹⁹	1795	SMR (in press operators and in bookbinders exposed to paper dust potentially containing talc)	1.0 (6)	0.35–2.18
Pulp and paper mill, Norway ²⁰		SIR (all workers with more than three years employment, at least 44% of which have been exposed to paper dust potentially containing talc)	1.4 (14)	0.70–2.16

OR, odds ratio; RR, relative risk; SIR, standardised incidence ratio; SMR, standardised mortality ratio.

APPENDIX D: ADAPTED IARC TABLES (2010)

Table D1: Cohort studies of mortality from and incidence of lung cancer in populations occupationally exposed to non-asbestiform talc

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	Cases/deaths	Relative risk (95% CI)	Adjustment factors; comments
Rubino <i>et al.</i> (1976), Germanesca and Chisone valleys (Piedmont), Italy	1992 male talc workers (1514 miners, 478 millers) employed >1 year in talc exposed job during 1921–1974; hired 1921–1950; mortality follow-up, 1921–74; vital status, 90%; cause of death: 95% of exposed workers, 95% of controls	Occupational history from plant records; respirable dust measurements, 1948–1974; quantitative estimation of cumulative exposure for individual workers, expressed as summed product of duration (years) and exposure (million particles per cubic foot, mppcf); classification of workers into 3 levels of exposure	Lung, bronchus and trachea	All miners All millers <i>Miners (mppcf-years)</i> Level 1: 566–1699 Level 2: 1700–5665 Level 3: 5666–12750 <i>Millers (mppcf-years)</i> Level 1: 25–141 Level 2: 142–424 Level 3: 425–906	9 4 3 1 5 3 1 0	SMR 0.5 (0.2–0.9) 0.6 (0.2–1.6) 1.1 (0.6–1.7) 0.5 (0.7–2.3) 1.1 (0.4–1.3) 1.7 (0.3–4.9) 1.25 (0–7.0) –	Adjusted for age; comparison with unexposed, age-matched controls from neighbouring rural town; controls matched on vital status at date of entry into study; miners and millers exposed to a very pure form of talc; miners also exposed to inhalable silica; significantly elevated SMRs for silicosis with and without tuberculosis among miners; estimates increased with increasing cumulative exposure; no observed cases of mesothelioma; no smoking data for exposed workers or unexposed controls

Table D1 (Contd)							
Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	Cases/deaths	Relative risk (95% CI)	Adjustment factors; comments
Rubino <i>et al.</i> (1979), Germanesca and Chisone valleys (Piedmont), Italy	1678 male talc workers (1260 miners, 418 millers); mortality follow-up, 1946–74	Same exposure categories as Rubino <i>et al.</i> (1976)	Lung	All miners All millers <i>Miners (mppcf–years)</i> Level 1: 566–1699 Level 2: 1700–5665 Level 3: 5666–12750 <i>Millers (mppcf–years)</i> Level 1: 25–141 Level 2: 142–424 Level 3: 425–906	8 4 2 1 5 3 1 0	SMR 0.5 (0.2–0.9) 0.7 (0.2–1.7) 0.5 (0–1.9) 0.2 (0.5–1.2) 0.6 (0.2–1.4) 2.0 (0.4–5.8) 0.7 (1.7–3.7) –	Re-analysis of cohort reported in Rubino <i>et al.</i> (1976); SMRs recalculated using national death rates instead of comparison with neighbouring rural population; national death rates available only from 1951 onward; rates for 1951 were applied for 1946–50
Selevan <i>et al.</i> (1979), Vermont, USA	392 white male talc workers (163 miners, 225 millers) employed >1 year between 1940 and 1969; mortality follow-up: date of first radiogram, 12-month employment anniversary or January 1940, whichever was later; follow-up through 1975; vital status: 99%; cause of death: 94%	Historical insufficient information to calculate cumulative exposure histories; cohort classified into two work areas: mining and milling.	Respiratory cancer	Total cohort Millers Miners	6 2 5	SMR [1.6 (0.6–3.5)] [1.0 (0.1–3.7)] [4.3 (1.4–10.1)]	Adjusted for age, sex, race, calendar year; US death rates: 1940–67; linear extrapolation for all causes of death: 1967–69. Vermont death rates for specific causes of death: 1949–75; workers selected from annual radiographic survey of dusty trades; no data on smoking habits for millers or miners; exposure to radon daughters in mine; radiographic evidence of pneumoconiosis in most workers who died from non-malignant respiratory disease

Table D1 (Contd)							
Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	Cases/deaths	Relative risk (95% CI)	Adjustment factors; comments
Wergeland <i>et al.</i> (1990), northern and western Norway	389 male talc-exposed workers (94 miners, 295 millers) employed >1 year in mine (1944–72) or >2 years in mill (1935–72); mortality and cancer incidence follow-up; 1953–87	Subjective assessment of exposure by experienced colleagues; workers classified by total duration of employment in jobs with low, medium, high and unknown exposure	Lung	<i>Total cohort</i>	6	SIR 0.9 (0.3–2.0)	Adjusted for age, smoking (miners only); national death rates: 1953–87; main minerals in mined talc deposit were talc and magnesite; 90% of raw material for mill from mine; 10% from India; no information on smoking habits for millers; smoking habits for miners above national average; low levels of exposure to radon daughters
				<i>Miners</i>	2	[1.6 (0.2–5.7)]	
				<i>Millers</i>	4	[0.8 (0.2–2.0)]	
				<i>Years employed</i>			
				<i>1–4</i>	0	–	
				<i>5–19</i>	3	[1.0 (0.2–3.0)]	
				<i>>20</i>	3	[1.0 (0.2–3.0)]	
				<i>Years since first employment</i>			
				<i>1–19</i>	2	[1.1 (0.1–4.1)]	
				<i>20–29</i>	1	[0.5 (1.3–2.8)]	
				<i>>30</i>	3	[1.1 (0.2–3.2)]	

Table D1 (Contd)							
Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	Cases/deaths	Relative risk (95%CI)	Adjustment factors; comments
Wild (2000), Luzenac, France	1160 talc workers (1070 men, 90 women) actively employed in 1945 or hired during 1945–94 and employed >1 year; mortality follow-up, 1945–96; vital status: 97%; cause of death: 74% pre-1968 and 98% post-1968	Exposures assessed for case–control study; semi-quantitative, site-specific job-exposure matrix based on personal dust measurements (1986 onwards) and subjective assessments by experienced workers; workers assigned to four categories of exposure: no exposure, ambient (<5 mg/m ³), medium (5–30 mg/m ³) and high(>30 mg/m ³); exposure prior to hiring also coded: none, probable exposure to quartz, certain exposure to quartz, exposure to other carcinogens.	Lung	<i>Male talc workers</i> Post-1968 (regional rates) Post-1968 (national rates) Men <60 years of age Latency period <20 years Duration of employment <10 years	 21 21 7 5 8	SMR 1.2 (0.8–1.9) 0.9 (0.6–1.4) 2.0 [0.8–4.0] 2.4 [0.8–5.6] 2.1 [0.9–4.1]	Adjusted for age, sex, smoking, prior exposure to quartz (case–control study only); partial overlap of study population with Leophonte <i>et al.</i> (1983) and Leophonte and Didier (1990); extent of overlap unknown; national mortality rates applied: pre- and post-1968; regional mortality rates applied: post-1968: excess mortality from lung cancer disappeared when national rates applied

Table D1 (Contd)							
Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	Cases/deaths	Relative risk (95% CI)	Adjustment factors; comments
Wild (2000) (contd)	Nested case-control study: lung cancer, non-malignant pulmonary disease and stomach cancer; three randomly selected controls per case; lung cancer: 23 cases, 67 controls	Cumulative exposure estimates (mg/m ³ -years) for individual workers	Lung	Unexposed <100 mg/m ³ -years 100-400 mg/m ³ -years 400-800 mg/m ³ -years >800 mg/m ³ -years Per 100 mg/m ³ -years	6 5 6 3 3 23	Odds ratio 1.0 1.4 2.2 0.7 0.9 1.0 (0.9-1.1)	Unadjusted odds ratio; no increasing trend with increasing cumulative exposure; information on smoking habits available for 52% of cases and 75% of controls. Assumes a linear trend
Wild <i>et al.</i> (2002), Luzenac, France (1 site), and Styrian Alps, Austria (4 sites)	Austrian cohort: 542 male talc workers employed >1 year during 1972-95; mortality follow-up, 1972-1995; vital status: 97%; French cohort: as described under Wild (2000)	Austrian cohort: semi-quantitative, site-specific job-exposure matrix based on personal dust measurements (1988-92) and descriptions of workplaces from management and long-term workers; workers assigned to four categories of exposure: no exposure, ambient (<5 mg/m ³), medium (5-30 mg/m ³) and high (>30 mg/m ³); other exposures coded: quartz, other carcinogens, underground work	Lung	French cohort Austrian cohort	21 7	SMR 1.2 (0.8-1.9) 1.1 (0.4-2.2)	Adjusted for age, calendar year, smoking, exposure to quartz, exposure to other carcinogens, underground work (case-control study); study population overlaps with that of Wild (2000); French SMRs calculated by comparison with regional rates, 1968-95; Austrian SMRs calculated by comparison with regional rates, 1972-1995; Austrian smoking information obtained from unpublished mortality studies on pneumoconiosis, from colleagues, from workers' compensation records; no missing information on smoking habits in Austrian cohort

Table D1 (Contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	Cases/deaths	Relative risk (95% CI)	Adjustment factors; comments
Wild <i>et al.</i> (2002) (contd)	Nested case-control study: lung cancer, non-malignant respiratory disease; three randomly selected controls per case; lung cancer: 23 cases, 67 controls (France); 7 cases, 21 controls (Austria)	Cumulative exposure estimates (mg/m ³ -years) assigned to individual workers by physician using work histories abstracted from company records	Lung	Unexposed ≤100 mg/m ³ -years 101-400 mg/m ³ -years 401-800 mg/m ³ -years >801 mg/m ³ -years Per 100 mg/m ³ -years	9 6 7 5 3 30	Odds ratio 1.0 0.9 1.1 0.6 0.7 1.0 (0.9-1.1)	Unadjusted odds ratio; no trend observed with increasing cumulative exposure; trend not affected by adjusting for smoking, quartz exposure, underground work or by lagging the exposure estimate. Assumes a linear trend
Coggiola <i>et al.</i> (2003), Piedmont, Italy	Cohort of 1974 male talc workers employed >1 year in mine or mill during 1946-95; mortality follow-up, 1946-95; loss to follow-up, 9%; analysis based on 1244 miners, 551 millers	Detailed job histories from plant records; workers classified on basis of job held (miner versus miller), duration of exposure (years) and time since first exposure (years)	Lung cancer	Total cohort Miners Millers <i>Years since first exposure</i> <20 20-30 >30	44 33 11 6 10 28	SMR 0.9 (0.7-1.3) 1.1 (0.7-1.5) 0.7 (0.3-1.2) 1.1 (0.4-2.3) 1.0 (0.5-1.8) 0.9 (0.6-1.3)	Adjusted for age, calendar period; study population overlaps with that of Rubino <i>et al.</i> (1976, 1979); national death rates used for pre-1970 period; rates for early 1950s used for 1946-49; regional rates used for 1970-95, except for cancers of oral cavity, oesophagus and suicide (regional rates unavailable, national rates used); no information on smoking habits; no variation in lung cancer by duration of exposure

CI, confidence interval; mppcf, million parts per cubic foot; SIR, standardized incidence ratio; SMR, standardized mortality ratio

Table D2: Cohort studies of mortality from and incidence of lung cancer in workers occupationally exposed to non-asbestiform talc in user industries

[illegible]